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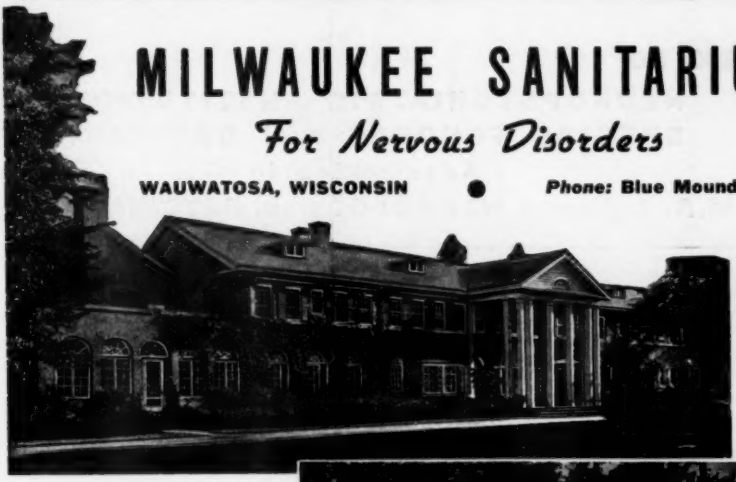

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ABSOLUTE MEASUREMENT OF THE VIBRATORY THRESHOLD

E. C. GREGG Jr., Ph.D.
CLEVELAND

FOR MANY years the appreciation of vibration has been used in the study and diagnosis of various neurologic disorders.[1] Up to the present time both the tuning fork and electrical vibrators [2] have been used for such determinations. However, while the latter represent a vast improvement over the former, the attendant errors in both have restricted their use to disorders that produce only large changes in the vibratory threshold. Furthermore, such instruments have been incapable of absolute calibration and as a result have been limited to relative studies. Recent investigations on certain neurologic disorders [3] and the effect of analgesics and other drugs have again served to emphasize the importance of the vibratory threshold, and it is the purpose of this paper to describe an instrument and a technique that allow the precise measurement of this threshold on an absolute scale.

PHYSICAL DESCRIPTION

While it is not the purpose of this paper to discuss either the modality or the particular mechanism involved in the perception of vibration, it is obvious that any technique of measurement must involve some sort of a vibrating body held against the subject. In the case of the tuning fork, it has been standard practice to start the fork at a given amplitude of vibration and to measure the time for the vibratory sensation to disappear. Since such a time decay depends on both the initial amplitude and the logarithmic decrement of the fork, it is obvious that the errors involved are enormous, even for an experienced operator using the same fork on the same test spot. Under these circumstances, errors in measurement may be on the order of 50 to 100%, and under some circumstances of comparative measurements errors on the order of 300% are not unusual.

Another complaint against the tuning fork is that the time of decay to a threshold bears no linear relation to the amplitude, so that comparative measurements are

From the Case Institute of Technology.

This work was supported by a grant from the Whitehall Pharmacal Company.

1. Gordon, I.: The Sensation of Vibration, with Special Reference to Its Clinical Significance, J. Neurol. & Psychopath. **17**:107, 1936. Fox, J. C., and Klemperer, W.: Vibratory Sensibility: A Quantitative Study of Its Thresholds in Nervous Disorders, Arch. Neurol. & Psychiat. **48**:622 (Oct.) 1942.

2. Known as biothesiometers, or pallesthesiometers (Laidlaw, R. W., and Hamilton, M. A.: Threshold of Vibratory Sensibility as Determined by the Pallesthesiometer, Bull. Neurol. Inst. New York **6**:494, 1937).

3. Frohring, W. O., and others: Changes in the Vibratory Sense of Patients with Poliomyelitis, Am. J. Dis. Child. **69**:89 (Feb.) 1945. Toomey, J. A., and others: Vibratory Threshold in Normal Persons and Poliomyelitis Patients as Affected by Moist Heat and Infrared Rays, Arch. Phys. Med. **27**:327, 1946.

rendered very difficult. A further factor, not to be overlooked, is that vibratory "adaptation" has been shown to exist,[4] and since the tuning fork starts at the high amplitudes and falls to lower values, the shape of the subject's adaptation curve should be taken into account.

On the other hand, the technique of driving an electrical vibrator with alternating current and increasing the amplitude of vibration until a threshold is reached has reduced these instrumental errors to between 10 and 40%. Other than the usual subjective errors, which are on the order of 5%, and which will be discussed later, common instrumental errors associated with electrical vibrators may be listed as follows:

1. Changes in acoustic impedance, or "stiffness," offered to the vibrator by various test areas. Such changes in impedance are reflected back to the driving source and actually alter the amplitude of vibration for a given driving power. For example, with an electrical vibrator run at the same voltage, the amplitude of vibration changed by 20% when a bony area was substituted for a fleshy one. Since the amplitude of motion is the critical vibratory-threshold parameter, the use of voltage (or current) as a measure of this amplitude leads to errors in relative thresholds when various test areas are used.

2. Time changes in vibrator characteristics. Both tuning forks and electrical vibrators will change characteristics with time, so that even if such a device were calibrated under a given set of circumstances, this calibration could change. Variations on the order of 10% have been noticed in certain vibrators merely as the result of heating during one test run. Aging over a long period will change the characteristics even more seriously.

3. Changes in test conditions, such as holding pressure and operator technique. Closely allied to the changes in acoustic impedance offered by various test areas are changes in the force generated by a given vibrator with the magnitude and direction of the pressure holding the vibrator button against the subject. This means simply that the amplitude of vibration at a given driving power will change with the holding pressure because of the vibrator characteristics alone. While an experienced operator will hold the vibrator against the patient with approximately the same pressure, this effect can be enormous (about 50%) in some vibrators.

While there are other, less important instrumental errors that occur in such measurements, it is obvious that one solution to the entire problem is to construct a device that would monitor the motion of the vibrator and yet be entirely independent of it. Such a device not only would minimize all the instrumental errors involved but would also be capable of calibration in absolute units—a feature of great importance not only in comparing various disorders and test areas but also in correlating the results of other investigators.

INSTRUMENTATION

The equipment found to be most satisfactory consists simply of a standard electrical vibrator with an amplitude-measuring device fastened directly to the vibrator head. This amplitude "monitor" converts the motion of the vibrator

4. Aring, C. D., and Frohring, W. O.: Apparatus and Technique for Measurement of Vibratory Threshold and of Vibratory Adaptation Curve, J. Lab. & Clin. Med. **28**:204, 1942.

head into a minute electrical signal, which is then measured by means of an electronic voltmeter. Figure 1 is a schematic circuit of the over-all electrical details, while Figure 2 is a photograph of the vibrator, monitor, and associated equipment. A variac® (continuously variable transformer) allows the vibrator amplitude to be increased smoothly from zero to full vibration. A scale selector on the voltmeter then provides a means of monitoring this vibration over the complete range.

The vibration-measuring device shown in Figure 3 consists of a bender-type potassium and sodium tartrate (rochelle-salt) crystal arranged as a cantilever, free

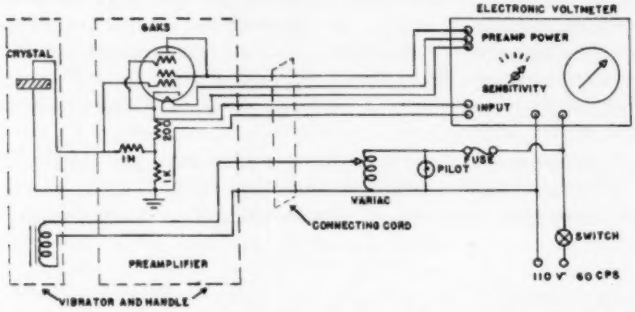

Fig. 1.—Schematic circuit of vibrator and associated vibration-monitoring equipment.

Fig. 2.—View of complete vibratory-threshold apparatus.

at one end and clamped at the other to the vibrator button. Owing to the inertia of the free end of the crystal, any motion of the vibrator rod perpendicular to the plane of the crystal results in an alternating voltage appearing on the crystal surfaces. The crystal and electrostatic housing were designed to present a minimum (negligible) load to the vibrating system. A suitable amplifier and vacuum-tube voltmeter then allow the generated voltage to be measured fairly accurately.[5]

5. For example, the model 300A electronic voltmeter manufactured by Ballantine Laboratories.

It should be mentioned here that potassium and sodium tartrate crystals are characterized by a fairly large dependence of sensitivity on temperature unless they are terminated by a high impedance. Since 4 ft. (1.6 m.) of shielded cable was found to be an excessive capacitative load under these circumstances, a special vacuum-tube preamplifier was constructed which presented a high impedance to the crystal and a low impedance to the connecting cable, with little loss in voltage sensitivity. This preamplifier is shown schematically in Figure 1, while physically it is placed in the handle of the vibrator shown in Figure 2.

A less obvious reason for the preamplifier is that with large vibratory amplitudes, which are necessary for some investigations, the crystals fatigue and crack unless they see a high electrical impedance. The use of the preamplifier in the instrument shown increased the life of the crystal element from about 50 hours, under excessive vibration, to over one year of almost daily use without replacement up to the time of this report.

Cursory analysis has shown that the crystal voltage generated is a direct measure of the amplitude of vibration. Furthermore, the inertial feature of the device guarantees that the amplitude measured is that due to the relative motion

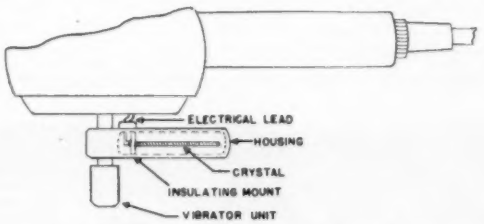

Fig. 3.—Schematic section of vibration monitor.

of the button and test spot, and not that of the button with respect to the vibrator housing. The two types of motion may differ in some cases by as much as 30%. The former is, of course, desired.

ABSOLUTE CALIBRATION

While the crystal pickup allows a direct measure of the amplitude of vibration, the units are in volts, and not centimeters of motion of the vibrating head.

In order to calibrate the pickup in absolute terms of amplitude, points of light reflected from the vibrating arm were observed with a micrometer microscope. When the arm was in vibration, these points became "lines," with a length equal to twice the amplitude of vibration. The micrometer microscope then allowed one to measure this "line" with a high degree of accuracy while measuring the voltage output of the crystal. Such data give immediately the sensitivity of the instrument in centimeters of motion (amplitude) per volt output of the crystal. For the particular instrument shown, the monitor sensitivity was found to be 2.46×10^{-2} cm./volt at 120 cps.

The accuracy of relative vibration measurements with this type of instrument is on the order of 1%, while that of the absolute calibration is about 5%.

VIBRATOR CHARACTERISTICS

While the amplitude of motion may be determined to a high degree of accuracy with the monitor just described, another important parameter which must not be overlooked is the frequency of vibration. This frequency is determined not only by the frequency of the driving current, but also by the construction of the vibrator. There are in general two types of vibrators available: those with a permanent magnetic field and those without. The former are styled after loud-speaker motors, while the latter are generally available as massage units.

It can be shown that if no permanent magnetic field is present the frequency of the vibrating arm will be twice that of the applied frequency and the amplitude of motion will be proportional to the square of the applied current. On the other hand, if a permanent magnetic field is present, the frequency of vibration will be the same as that applied and the amplitude will be proportional to the current. In both cases the applied voltage bears a fixed relationship to the current at a given frequency and may be used as a measure of the amplitude at that frequency as long as the acoustic impedance and other aforementioned parameters are constant.

In these investigations, simple vibrators (Fig. 2) with no permanent field were used because of their ruggedness at high amplitudes and the ease and inexpensiveness of replacement. A check on this type of vibrator with the vibration monitor showed both the voltage-squared relationship and the frequency-doubling effect to hold true. The latter was shown by observing the wave form of the crystal-monitor voltage on a cathode-ray oscilloscope. While a little 60-cycle signal was present, the second harmonic was predominant (approximately 95%). This means that if 60-cps. current is applied to the vibrator shown in Figure 2, the arm will move back and forth 120 times a second. While the frequency of vibration would have no effect on relative thresholds all made under the same conditions, absolute measurements and comparisons of data taken by different experimenters would be of little value unless the frequency were listed. This follows, since the threshold is undoubtedly a function of frequency.[6]

SUBJECTIVE ERRORS AND NORMS

Any investigation involving the response of a subject necessarily has errors present owing to indecision on the part of the subject as to the exact end point. While they are caused by many separate psychological and environmental factors, it is the usual practice to consider them together as the "subjective error." In addition, a certain amount of judgment and response time on the part of the operator are involved, and these variations, too, are usually grouped with the subjective error. However, experience with several hundred subjects and several operators over the past two years has shown that the operator errors are negligible as compared with the over-all errors as long as the operators are conscientious and intelligent.

In taking data for the determination of subjective errors and norms, the usual practice is to select a test spot, raise the vibratory amplitude until a subjective response is obtained, and then lower the amplitude until the sensation disappears. The intensity of vibration is noted for both directions of change. This procedure,

6. The results of a preliminary investigation of the frequency dependence of the vibratory threshold will be given in a later paper.

then, is repeated several times by the operator in as short a time as possible, and the average of all observations is considered the vibratory threshold of the subject at that time. Table 1 lists sample observations of this sort on several subjects, and it is to be noted that the standard deviation from the average for any one run is about 2.5%. This figure is typical of observations on many subjects (over 100) and represents the accuracy of any given single observation under controlled conditions. The last qualification is added since certain psychological and environmental factors, to be mentioned later, have been found to affect this accuracy of a single observation.

With regard to how accurately a single observation represents the vibratory threshold, data taken at intervals of 10 min. on the same subject indicate relatively large variations of the threshold with time, even though each single observation has a high accuracy. Figure 4 shows sample curves of threshold variations with time for several subjects under controlled conditions. Such curves are termed "norms" and are used for reference purposes when determining the action of any particular drug or external agent on the threshold.

Figure 5 is a frequency histogram of the percentage deviation from average for 1,200 observations on 100 subjects. In this graph, the deviation is from an

TABLE 1.—*Sample Observations of the Vibratory Threshold of One Subject* *

Run	Readings (Arbitrary Units)								Average Reading
1	10.0	10.2	10.2	10.5	10.8	10.5	10.5	....	10.40
2	10.0	10.0	10.2	10.5	11.0	10.8	10.5	10.5	10.44
3	11.0	11.2	10.8	10.8	10.5	10.2	10.2	10.5	10.65
4	10.0	10.8	10.2	10.2	10.5	10.2	10.8	10.5	10.40
5	10.0	10.0	10.2	10.5	10.2	10.2	10.2	....	10.20

* Each run is made in as short an interval of time as possible (about one minute), while the separate runs are 10 min. apart.

average for each subject determined by 30-min. total observation (similar to Figure 4) and evaluated at 10-min. intervals after the start of the test. Such data were repeated three times for each subject, with relatively long intervals (several weeks) between each run. This method of treatment is warranted, since it is obvious that each subject has a different absolute threshold. It is to be noted that the curve is Gaussian, with a probable error of about 3%. This 3%, then, represents the probable error of the norm under controlled conditions and may be used as a criterion for any changes that might be induced in the threshold by external agents or drugs.

Of the many factors that influence the time variations in the threshold, the following have been found to be the most important:

1. Intelligence of the subject. A fairly intelligent subject is required in order that he may understand not only the nature of the test but also the importance of distinguishing the end point clearly and quickly. Experience has shown that in general only subjects of college-level intelligence or greater give consistent data with small probable errors. Other, less intelligent subjects have large time variations in threshold, even though the single observations are seemingly accurate. While this may be significant in itself, these subjects are not suited for group tests on the effects of various drugs or external agents on the threshold.

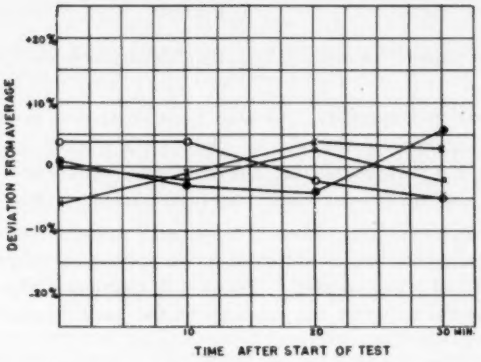

Fig. 4.—Representative curves showing variations in the vibratory threshold with time.

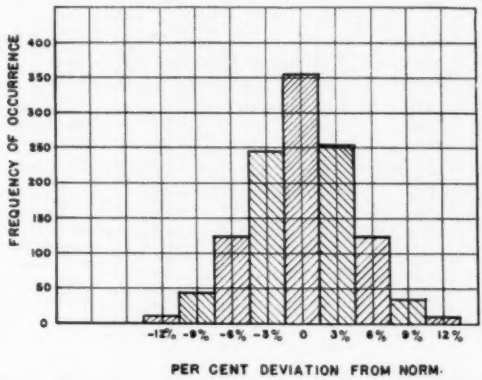

Fig. 5.—Histogram illustrating the spread of 1,200 observations on the norms of 100 subjects.

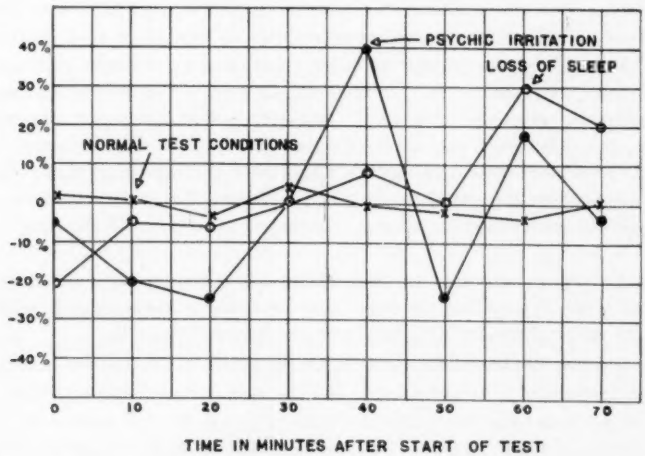

Fig. 6.—Influence of loss of sleep and psychic irritation on the vibratory threshold. Noise and extremes in temperature and humidity create the same large variations in the vibratory threshold.

2. Noise. Excessive noise distracts the subject's attention and, of course, results in poor readings.

3. Temperature and humidity. As with noise, extremes in temperature and humidity cause deviations in the norms. These effects, while noticeable, are not excessive, and it has been found that any reasonably comfortable room is satisfactory. This is also important from the operator's point of view.

4. Fatigue. This naturally reduces the subject's enthusiasm for the test and causes inattention on his part. In Figure 6 the norm of a subject when rested is compared with that when fatigued. Objective distractions and mental problems have also been found to affect the readings in the same manner. This is also shown in Figure 6.

If precautions are taken with respect to these factors, the norms become remarkably consistent with the probable errors listed previously.

TABLE 2.—*Absolute Vibratory Thresholds of Various Body Areas, Expressed in Microns (10^{-4} Cm.) of Motion at 120 Cycles per Second*

Forehead	6.16	Trunk, anterior		Calf, distal side	2.96
Cheekbone	7.90	T2	2.96	First toe base	0.616
Jaw bone	6.16	T4	2.34	First toe tip	0.838
Sternal notch	2.21	T6	3.70	Toe	
Shoulder	7.40	T8	6.41	2	1.11
Upper arm	1.72	T11	9.11	3	1.38
Forearm	6.90	Trunk, posterior		4	1.12
Wrist	0.780	T2	1.47	5	0.986
Finger tip		T4	1.97	Instep	0.666
1 (thumb)	0.370	T6	5.42	Edge of tibia	0.780
2	0.420	T8	14.7	Side of knee	3.50
3	0.395	T11	6.16	Calf, proximal side	2.95
4	0.320	7th vertebral spine	6.90	Sacrum	12.3
5	0.370	Thigh			
		L2	8.88		
		L3	6.66		

TEST-SPOT SELECTION AND VARIATIONS IN ABSOLUTE THRESHOLD

Rather exacting tests showed that the inherent subjective errors changed with the test areas. That this would be true is obvious from the fact that, since vibration is an acoustic effect, different areas involve different degrees of acoustic transmission, and hence different receptor areas or volumes. For example, readings from the forehead were found to be extremely erratic due to the subject's difficulty in distinguishing between "hearing" and "feeling." While this is an extreme case, other test-spot differences, such as bone proximity, are obviously important. It was found that of all the areas investigated, a spot over the right quadriceps one-third the distance between the upper part of the patella and the greater trochanter gave results with the least subjective errors. This spot was used for all the data reported above.

Table 2 shows the absolute threshold of various test spots for a normal subject. It is worth while to note that the finger tips can detect a motion of 3.2×10^{-5} cm. and that the range of maximum to minimum sensitivity is about 46 : 1.

Table 3 shows the long-time variations in threshold of one subject, and Table 4 lists the thresholds for different subjects at a test spot over the right quadriceps area.

It is to be noted that the particular subject tested did not show a very great change in threshold with long-time intervals and that, with the exception of Subject

22, there was not too great a spread among several subjects. This has been found to be generally true for almost all the subjects who lend themselves to this type of subjective test. A further study of normal subjects, however, should certainly prove fruitful.

The influence of the vibrator-holding pressure on the threshold was investigated and found to be negligible as long as too little pressure for adequate test-button contact and excessive (almost painful) pressure were avoided. Also, measurements with vibrator buttons of different diameters (ranging from ⅛ to 1½ in. [0.32 to 3.8 cm.]) showed that the threshold is independent of area and hence that there is no spatial summation of this particular modality.

TABLE 3.—*Observations on the Threshold of One Subject at Several Different Times* *

	Relative Time of Observation, in Min., During Each Run												
Date of Run	0	10	20	30	40	50	60	70	80	90	100	110	120
5/29/49	11.5	11.5	11.5	11.85	11.65	11.55	11.5	11.45	11.65	11.45	11.85	11.45	11.65
1/11/50	11.5	12.0	11.5	12.0	12.0	11.5	.....	.....	.....	.....	.....	.....	.....
1/18/50	11.5	11.5	12.0	11.75	12.0	11.25	.....	.....	.....	.....	.....	.....	.....
5/ 5/50	12.0	11.5	11.5	12.0	11.5	11.0	11.5	11.5	11.0	11.5	11.0	12.0	.....

* Each point is an average of several observations and is expressed in arbitrary units.

TABLE 4.—*Thresholds of Various Subjects Measured at the Same Test Spot and Under Comparable Environments* *

	Relative Time of Observation, in Min., During Each Run												
Subject	0	10	20	30	40	50	60	70	80	90	100	110	120
7	10.5	9.75	9.5	9.6	10.3	10.0	10.0	9.8	10.0	10.2	10.0	10.0	....
5	10.4	10.44	10.65	10.4	10.2	....	....	....	....	....	....	....	....
24	12.0	12.0	12.0	12.0	11.5	12.0	11.0	11.0	12.2	11.0	....	....	....
23	13.0	12.5	13.0	13.0	13.5	13.0	12.5	....	....	....	....	....	....
21	10.0	10.2	10.0	10.5	10.0	10.2	10.0	10.2	....	....	....	....	....
22	3.35	3.2	3.3	3.2	3.1	3.2	3.1	3.0	2.8	2.8	....	....	....
8	11.5	11.5	11.5	11.85	11.65	11.55	11.5	11.45	11.65	11.45	11.85	11.45	11.65

* Each point is the average of several observations, and the readings are in arbitrary units.

SUMMARY

An instrument is described which will allow relative measurements of the vibratory threshold to within 1% and absolute determinations of the vibratory threshold to within 5%. This instrument measures the amplitude of vibration independent of variations in vibrator characteristics and changes in acoustic impedance. An analysis of sources of error in any vibratory-threshold determination is made; the effects and minimization of pertinent environmental factors are discussed. Data are presented concerning the absolute threshold of various areas in an individual subject, time variations in thresholds, and other factors pertinent to determination of the vibratory threshold.

University Circle (6).

Mr. A. A. Hruschka furnished some of the design details and construction, and the late Dr. J. A. Toomey and Dr. J. Seifter made some of the measurements reported in this paper.

ANALYSIS OF PROGNOSTIC FACTORS IN INSULIN THERAPY

MAX COHEN, M.D.
COATESVILLE, PA.

DEEP insulin-shock therapy has been established as an accepted treatment for schizophrenia and certain allied disorders for over a decade. Many publications indicate that higher ratios of satisfactory results are obtained from insulin-treated patients than from controls, particularly if the treatment is administered early in the course of the disease.[1] The purpose of this investigation is to determine what factors, if any, are of prognostic significance with reference to this form of therapy.

MATERIAL

One thousand patients, all males, were treated with deep insulin-shock therapy over a three-year period. The selection of these patients was not on the basis of probable prognosis but entirely on the presentation of a diagnosis of schizophrenia or an allied functional psychosis. Of these, 1,000 patients the data on 639 were subjected to final analysis. Excluded were 52 patients who did not complete the course of treatment because of complications, 1 who died of prolonged coma (0.1% mortality), 49 who received a second course of therapy, and 259 who were admitted prior to the establishment of an insulin-therapy service and who, although treated, do not appear in the statistical analysis because insulin therapy was not available to them on admission to the hospital. That patients with disease of identical severity were treated over the years can be seen from these figures: Of all neuropsychiatric patients admitted during 1946, 40% received insulin therapy; during 1947, 39%; during 1948, 39%, and during 1949, 40%. These figures pertained despite variations in the total number of neuropsychiatric admissions for each year.

METHOD

In order to make statistical analysis as simple as possible, the following classification of the results of therapy was used: 1. A plus (+) result was obtained if the patient left the hospital within two months of completing treatment and did not return within 18 mo. 2. A minus (—) result was obtained if the patient did not leave the hospital for 18 mo. after treatment. 3. A plus-minus (±) result was obtained if the patient either left the hospital more than two months after treatment or, having left, returned to the hospital within 18 mo.

It may be objected that this is an arbitrary categorization and may not have any close relation to the patient's actual mental state. However, I am attempting to find a relative

---

All somatotyping was performed by Dr. S. Dinenberg, Chief of Continued Treatment Service, Veterans Administration Hospital, Coatesville, Pa.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Bond, E. D., and Shurley, J. T.: Insulin Therapy and Its Future, Am. J. Psychiat. **103**:338 (Nov.) 1946. Hinko, E. N., and Lipschutz, L. S.: Five Years After Shock Therapy, ibid. **104**:387 (Dec.) 1947. Paster, S., and Holtzman, S. C.: A Study of One Thousand Psychotic Veterans Treated with Insulin and Electric Shock, ibid. **105**:811 (May) 1949. Palmer, D. M.; Riepenhoff, M. D., and Hanahan, P. W.: Insulin Shock Therapy, a Statistical Survey of 393 Cases, ibid. **106**:918 (June) 1950. Bond, E. D., and Rivers, T. D.: Further Follow-Up Results in Insulin Shock Therapy, ibid. **99**:201 (Sept.) 1942.

difference between these groups and statistically any reasonable definition can be made provided that one adheres to it throughout and remains primarily interested, not in absolute magnitudes, but only in the differences.

All patients were under the direct supervision of the same physician for the period of this study, and all were given a standardized regimen of 10-wk. treatment with the rapid-induction method, as developed by Shurley and others,[2] with identical definitions of coma, stupor, etc. In all, 17 factors were subjected to analysis by means of the chi-square (χ^2) technique. A value for P of over 5% indicates that no significant differences exist; a value for P of under 1% indicates that significant differences do exist, and a value for P between 1% and 5% indicates that a borderline situation exists as regards significant differences.

The factors analyzed were (1) race, (2) marital status, (3) previous course of electric-shock therapy, (4) religion, (5) number of days of treatment, (6) number of coma days, (7) total hours of coma, (8) average daily dose of insulin, (9) highest dose of insulin given, (10) number of insulin convulsions, (11) number of electric-shock treatments combined with insulin, (12) somatotype, (13) diagnosis, (14) weight gained, (15) age at onset of psychosis, (16) age at insulin therapy, and (17) length of time sick.

RESULTS

The analyses of these 17 factors are presented in Tables 1 to 17.

TABLE 1.—*Race*

	+	±	−	No.
Negro	15	22	32	69
White	162	161	247	570
Total	177	183	279	639
	$\chi^2 = 1.39$		$P = 30\text{-}50\%$	

P is greater than 5%, and therefore the response to therapy is independent of whether the patient is white or Negro.

TABLE 2.—*Marital Status*

	+	±	−	No.
Married	44	47	61	152
Single	133	136	218	487
Total	177	183	279	639
	$\chi^2 = 1.07$		$P = 50\text{-}70\%$	

P is greater than 5%, and therefore the response to therapy is independent of whether the patient is single or is other than single (married, divorced, separated, widower).

TABLE 3.—*Previous Course of Electric-Shock Therapy*

	+	±	−	No.
Course	65	77	109	251
None	112	106	170	388
Total	177	183	279	639
	$\chi^2 = 1.07$		$P = 50\text{-}70\%$	

P is greater than 5%, and therefore the response to therapy is independent of whether or not the patient had a previous course of electric-shock therapy.

2. Shurley, J. T.: Insulin Shock Therapy in Schizophrenia, Veterans Administration Technical Bulletin TB 10-501, April 16, 1948.

TABLE 4.—*Religion*

	+	±	−	No.
Catholic	95	84	140	319
Protestant	73	88	119	280
Jewish	9	9	14	32
None	0	2	6	8
Total	177	183	279	639
	$\chi^2 = 6.24$		$P = 30\text{-}50\%$	

P is greater than 5%, and therefore the response to therapy is independent of the patient's religious preference.

TABLE 5.—*Number of Days of Treatment*

	+	±	−	No.
44 or less	10	7	12	29
45-49	21	16	22	59
50-54	30	31	39	100
55 or more	116	129	206	451
Total	177	183	279	639
	$\chi^2 = 4.62$		$P = 50\text{-}70\%$	

P is greater than 5%, and therefore the response to therapy is independent of the number of days of treatment given, provided it is between 40 and 60.

TABLE 6.—*Number of Coma Days*

	+	±	−	No.
39 or less	41	35	42	118
40-44	46	47	58	151
45-49	58	73	111	242
50 or more	32	28	68	128
Total	177	183	279	639
	$\chi^2 = 12.31$		$P = 5\text{-}10\%$	

P is greater than 5%, and therefore the response to therapy is independent of the number of coma days, provided it is between 35 and 55.

TABLE 7.—*Total Hours of Coma*

	+	±	−	No.
19 or less	16	21	22	59
20-24	51	47	60	158
25-29	75	69	129	273
30 or more	35	46	68	149
Total	177	183	279	639
	$\chi^2 = 7.22$		$P = 30\text{-}50\%$	

P is greater than 5%, and therefore the response to therapy is independent of the number of total coma hours, provided it is between 15 and 35. This figure represents hours of deep coma, if less deep states of coma are included, the number of hours would be about doubled. The lack of significance, however, would remain unchanged.

TABLE 8.—*Average Daily Dose of Insulin*

Units	+	±	−	No.
199 or less	58	45	91	194
200-399	67	83	121	271
400 or more	52	55	67	174
Total	177	183	279	639
	$\chi^2 = 6.05$		$P = 10\text{-}20\%$	

P is greater than 5%, and therefore the response to therapy is independent of the average daily dose of insulin required, provided sufficient is given to obtain the number of coma days and coma hours previously indicated.

TABLE 9.—*Highest Dose of Insulin Given*

Units	+	±	−	No.
799 or less	52 (32%)	44 (27%)	65 (40%)	161
800-1,200	81 (24%)	89 (26%)	166 (49%)	336
1,201 or more	44 (31%)	50 (35%)	48 (34%)	142
Total	177	183	279	639
	$\chi^2 = 12.23$		$P = 1\text{-}2\%$	

P is between 1% and 5%, and therefore a borderline situation of significance exists. However, further analysis of the percentages given does not reveal a definite trend, and actually these borderline differences can be attributed to chance. The response to therapy may therefore be considered independent of the highest dose of insulin given.

TABLE 10.—*Number of Insulin Convulsions*

	+	±	−	No.
0	112	106	169	387
1	28	30	48	115
2	21	29	40	81
3 or more	16	18	22	56
Total	177	183	279	639
	$\chi^2 = 3.79$		$P = 70\text{-}80\%$	

P is greater than 5%, and therefore the response to therapy is independent of the number of insulin convulsions occurring, if any.

TABE 11.—*Number of Electric-Shock Treatments Given Combined with Insulin*

	+	±	−	No.
0	56 (39%)	53 (37%)	36 (25%)	145
1-5	14 (30%)	16 (34%)	17 (36%)	47
6-10	36 (26%)	44 (31%)	60 (43%)	140
11 or more	71 (23%)	70 (23%)	166 (54%)	307
Total	177	183	279	639
	$\chi^2 = 36.51$		$P = 0.001\%$	

P is much less than 1%, indicating a significant finding, and a consideration of the percentages indicates that an increase in the number of combined treatments is associated with poorer results. However, according to our procedure, combined therapy was given only to those patients who did not respond to insulin alone by the seventh week. Thus, a choice was made, only those being selected for combined

therapy who were most unlikely to respond at all. The statistics simply reveal that choice. Actually, no comment one way or another as to the value of combined therapy can be made.[3]

TABLE 12.—*Somatotype*

	+	±	−	No.
Ectomorphic-mesomorphic	15	15	24	54
Endomorphic-mesomorphic	7	13	13	33
Mesomorphic-ectomorphic	5	5	12	22
Mesomorphic-endomorphic	2	5	2	9
Predominantly mesomorph	5	7	4	16
Others	4	2	5	11
Total	38	47	60	145
	$\chi^2 = 8.33$		$P = 50\text{-}70\%$	

P is greater than 5%, and therefore the response to therapy appears independent of the patient's somatotype. Only 145 of the total group were somatotyped (Sheldon's method). However, many of the rarer somatotypes were not encountered, and some of those found were not in sufficient numbers to be of statistical significance. It may be that in those not encountered there are significant relationships, but this study would indicate that the response is independent of the somatotype.[4]

TABLE 13.—*Diagnostic Type*

	+	±	−	No.
Hebephrenic	25 (22%)	26 (23%)	62 (55%)	113
Catatonic	36 (30%)	34 (28%)	50 (42%)	120
Paranoid	74 (31%)	77 (32%)	91 (38%)	242
Other	42 (26%)	46 (28%)	76 (46%)	164
Total	177	183	279	639
	$\chi^2 = 10.32$		$P = 10\text{-}20\%$	

P is greater than 5%, and therefore the response to therapy appears independent of the diagnosis. Perusal of the percentages and finer analysis indicate that the hebephrenic type will do slightly less well and the paranoid type slightly better than the average. However, it would appear that a schizophrenic patient should not be withheld from or favored for treatment because of the diagnostic subtype. This appears to include patients with a disturbance diagnosed as other than schizophrenia (nonorganic) but with schizophrenic-like symptoms.

TABLE 14.—*Weight Gained*

Lb.	+	±	−	No.
0-9	9 (22%)	13 (32%)	19 (46%)	41
10-19	43 (23%)	49 (26%)	98 (52%)	190
20-29	52 (23%)	67 (29%)	109 (48%)	228
30-39	54 (40%)	41 (31%)	39 (29%)	134
40 and over	19 (41%)	13 (28%)	14 (30%)	46
Total	177	183	279	639
	$\chi^2 = 28.01$		$P = 0.05\%$	

3. Horwitz, W. A., and Kalinowsky, L. B.: Combined Insulin Coma and Electric Convulsive Therapy in Schizophrenia, Am. J. Psychiat. **104**:682 (May) 1948.

4. Kline, N. S., and Tenney, A. M.: Constitutional Factors in the Prognosis of Schizophrenia, Am. J. Psychiat. **107**:434 (Dec.) 1950.

P is less than 1%, indicating a significant relationship between response and gain in weight. Perusal of the percentages indicates that the relationship is not one in which increasing gain in weight is associated with an increasingly better response but, rather, that an abrupt change occurs at a gain in weight of 30 lb. (13.6 kg.). The data can actually be summarized by stating that patients who gain more than 30 lb. do significantly better than those who gain less than 30 lb. This finding appears independent of how long the patient has been sick, as demonstrated in Table 17. Either this finding remains unexplained, or the following hypothesis may be advanced: It is a common observation that patients who lose weight immediately prior to the onset of a psychosis have a better prognosis. In this group, insulin therapy will have a tendency toward increased gain in weight. This increased gain is associated with a better response, and the assumption is made that patients who lose weight during their illness will respond better than those who do not. There was no record of the patients' usual weight prior to illness. It would appear that this could easily be determined, and it is hoped that this can be done at a future date.[5]

TABLE 15.—*Age at Onset of Psychosis*

Years	+	±	−	No.
19 or less	19	20	18	57
20-24	67	63	94	224
25-29	52	64	80	196
30-34	25	24	60	109
35 or more	14	12	27	53
Total	177	183	279	639
	$\chi^2 = 12.70$		$P = 10\text{-}20\%$	

P is greater than 5%, and therefore the response to therapy is independent of the age of the patient at onset of psychosis, provided the age is between 18 and 40.

TABLE 16.—*Age at Time of Insulin Therapy*

Years	+	±	−	No.
19 or less	10 (40%)	9 (36%)	6 (24%)	25
20-24	54 (33%)	53 (32%)	59 (36%)	166
25-29	66 (28%)	65 (28%)	103 (44%)	234
30-34	30 (22%)	40 (29%)	66 (49%)	136
35 or more	17 (22%)	16 (21%)	45 (58%)	78
Total	177	183	279	639
	$\chi^2 = 17.24$		$P = 2\text{-}5\%$	

P is between 1% and 5%, and a borderline situation of significance exists. Perusal of the percentages indicates a definite trend toward a poorer response with increasing age. This, therefore can be considered a significant finding. If the older patient is at the time of insulin therapy the poorer will be the response, it must mean either (*a*) that the older a patient is at onset of psychosis, the poorer will be the response, or (*b*) that the older patients have had a longer time interval between onset of psychosis and insulin therapy. The former is not true, as shown in Table 15; hence the latter must be true, as is shown in Table 17.

5. Kalinowsky, L. B.: Variations of Body Weight and Menstruation in Mental Illness and Their Relation to Shock Treatments, J. Nerv. & Ment. Dis. **108**:423 (Nov.) 1948.

TABLE 17.—*Length of Time Sick Prior to Insulin Therapy*

Years	+	±	−	No.
0-1	80 (44%)	55 (30%)	47 (26%)	182
1-2	34 (24%)	42 (30%)	65 (46%)	141
2-3	23 (18%)	42 (33%)	63 (49%)	128
3-4	17 (19%)	22 (25%)	50 (56%)	89
4 or over	23 (23%)	22 (22%)	54 (55%)	99
Total	177	183	279	639
	$\chi^2 = 48.72$		$P = 0.0001\%$	

P is considerably less than 1%, and therefore the response to insulin is dependent on the length of time that has elapsed between onset of psychosis and insulin therapy. Perusal of the percentages indicates that those sick under one year do much better than those sick over one year. However, there is no significant difference between the various yearly intervals over one year. Table 17 can therefore be summarized by comparing patients sick under one year and those sick over one year. The former will do approximately twice as well as the latter.

This finding appears to be a basic one, and one may advance as a hypothesis that something increasingly irreversible happens during the first year or two of illness. This drop in reversibility during 12 mo. amounts to 20%, or approximately 2% per month. This is a fairly considerable drop for low over-all percentages and suggests that a delay of several months during the early months of illness can seriously affect the outcome. A similar delay after a year's illness would be relatively unimportant. This strongly suggests early treatment, with a minimum of delay.

CONCLUSIONS

Seventeen factors are subjected to statistical analysis in an attempt to discover prognostic criteria in insulin therapy.

Thirteen factors, some with certain limits, appear unimportant. These are race, marital status, previous course of electric-shock therapy, religion, number of treatment days, number of coma days, total hours of coma, average daily dose of insulin, highest dose of insulin given, number of insulin convulsions, somatotype, diagnosis, and age at onset of psychosis.

The value of combined therapy could not be determined because of choice exerted in selection of cases.

The response to insulin therapy decreases with age at the time of therapy because of increasing length of the time sick.

Patients who gain over 30 lb. (13.5 kg.) in weight will do approximately twice as well as those who gain under 30 lb. A hypothesis is advanced to explain this.

Patients sick under one year will do approximately twice as well as those sick over one year. It is suggested that insulin therapy be given as early as possible in the first year of illness.

STUDIES ON THE BLOOD-BRAIN BARRIER WITH RADIOACTIVE PHOSPHORUS

LOUIS BAKAY, M.D.
BOSTON

RADIOACTIVE isotopes are being used with increasing frequency to localize brain tumors. Either the locally increased permeability of the blood-brain barrier or the active metabolism of the tumors—it is not at present clear which—causes a higher concentration of some isotopes in the tissue of the neoplasm than in the normal brain. The investigations of Hevesy and Hahn [1] showed that only a small fraction of radioactive phosphorus (P^{32}), approximately 0.02% of the total amount, given parenterally, is deposited in the brain. This finding was considered evidence of a slow phosphorus turnover in the central nervous system. Lindberg and I,[2] working on the theory that the blood-brain barrier plays a decisive role in this phenomenon, injected P^{32} directly into the cerebrospinal fluid, bypassing the barrier, and found that this isotope would indeed accumulate rapidly in the brain. After such an injection into the cisterna magna (cisterna cerebellomedullaris) vigorous transphosphorylation took place, reaching its peak 30 min. after the injection, when a large percentage of the inorganic phosphorus could already be found incorporated into organic compounds. These findings were confirmed by Lindberg and Ernster,[3] and by Sacks and Culbreth.[4]

MATERIAL AND METHODS

The experiments were performed on 22 rabbits. The P^{32} was given intravenously to 5 rabbits; of the other 17, anesthetized with pentobarbital sodium the isotope was injected into the cisterna magna through a 22-gauge needle. To avoid excess pressure in the cerebrospinal fluid spaces, a volume of the clear fluid was withdrawn after the cisternal puncture—in some cases an amount equal to the volume which was later injected, in others somewhat less. The amount of fluid exchanged was usually 0.1 to 0.3 cc. and never exceeded 0.5 cc. The amount of cerebrospinal fluid removed was replaced with an aqueous solution of buffered, carrier-free radioactive phosphorus. To determine the amount of radioactivity injected, the difference between the total amount of cerebrospinal fluid and that of the blood plasma of the animals was taken into consideration, so as to obtain data of some quantitative value. A ratio of 20 : 1 for the two body fluids was estimated; according to the weight of the rabbits, 60 to 90 μc was given intravenously, or 3 to 4.4 μc intracisternally.

From the Department of Neurosurgery of the Massachusetts General Hospital.

1. Hevesy, G., and Hahn, L.: Turnover of Lecithin, Cephalin, and Sphingomyelin, K. Danske vidensk. selsk., biol. med. **15**:1, 1940.

2. Bakay, L., and Lindberg, O.: Studies on the Role of the Cerebrospinal Fluid in Brain Metabolism as Measured with Radioactive Phosphate, Acta physiol. scandinav. **17**:179-190, 1949.

3. Lindberg, O., and Ernster, L.: The Turnover of Radioactive Phosphate Injected into the Subarachnoid Space of the Brain of the Rat, Biochem. J. **46**:43-47, 1950.

4. Sacks, J., and Culbreth, G. G.: Phosphate Transport and Turnover in the Brain, Am. J. Physiol. **165**:251-257, 1951.

The animals were killed by intravenous injection of pentobarbital sodium or of air emboli 10 to 60 min. and 4 and 24 hr. after the injection of P^{32} into the cistern and 8 to 24 hr. after intravenous administration of P^{32}. The skull was opened and the brain immediately removed. In the animals in which P^{32} was administered cisternally, the brain was rinsed briefly in running water, then frozen in carbon-dioxide snow and kept constantly at —15 C. In our previous experiments [2] the frozen brain was divided according to a particular scheme, and the total phosphate content and trichloroacetic-acid-soluble phosphate esters were determined, as well as the corresponding radioactive impulses per phosphate atom (specific activity).

In the present work, cross sections of the brains were used for radioautography and the method of Steinberg and Selverstone [5] employed. With the aid of parallel blades, slabs of uniform thickness (2.5 mm.) were prepared from the frozen brains, applied to Eastman "no-screen" x-ray films and kept in the deep freeze. Microscopic frozen sections (thickness, 20 μ) were also used for contact radioautographs. The exposure time for the gross specimens varied from 24 to 144 hr., and that for the microscopic slides, from 8 to 30 days. After development of the gross radioautographs, the frozen brain sections were divided into about twenty pieces, according to the various densities shown by the autographs. The selected pieces were weighed, placed on aluminum planchets, dried under a heat lamp, and counted by scalers. The final data were computed in counts per minute per milligram of tissue.

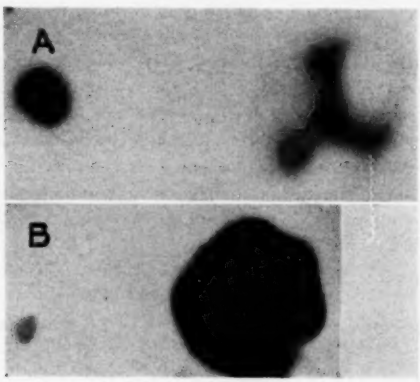

Fig. 1.—Radioautographs of pituitary glands (left), as compared with those of cross sections of corresponding brains (right). *A*, 24 hr. after intravenous administration of P^{32}; *B*, 30 min. after intracisternal injection of P^{32}. Exposure time, 112 hr.

RESULTS

Intravenously administered radioactive phosphorus reaches the maximum concentration in the brain from 12 to 24 hr. after the injection. By far the highest deposit of the isotope can be found in the pituitary gland, which shows about 60 times as much activity as the average white matter (Fig. 1*A*). The pineal gland, which according to Borell and Örström [6] contains a large deposit of P^{32}, was not

5. Steinberg, D., and Selverstone, B.: Radioautography of Cerebral Tumors Employing P^{32}, Proc. Soc. Exper. & Biol. Med. **74**:304-308, 1950.

6. Borell, U., and Örström, Å.: Metabolism in Different Parts of the Brain, Especially in the Epiphysis, Measured with Radioactive Phosphorus, Acta physiol. scandinav. **10**:231-242, 1945.

analyzed in these experiments. A higher accumulation of the P^{32} was found also in the choroid plexus and in the lining of the ventricles, including the central gray matter around the aqueduct, which showed five to seven times as much activity as the white matter; the cerebral and cerebellar cortex and the medulla oblongata showed a ratio of 3:1 (Fig. 2*A*). Other parts of the brain and spinal cord had a fairly equal low P^{32} content, with only about 1 to 2 counts per milligram.

After intracisternal administration, the map of the P^{32} deposits in the brain was entirely different. The peak of concentration was reached 30 to 60 min. after

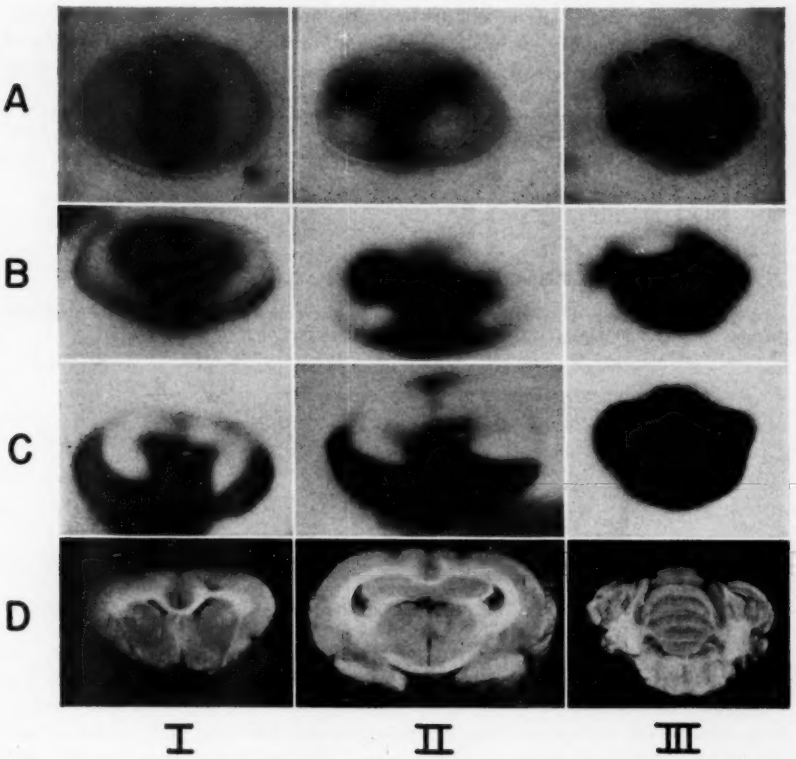

Fig. 2.—Radioautographs of cross sections of the frontal lobes (*I*), cerebrum (*II*), and cerebellum (*III*). *A I, II,* and *III*: 24 hr. after intravenous injection of P^{32}; exposure, 144 hr. *B I, II, III*: 10 min. after intracisternal administration of P^{32}; exposure, 46 hr. *C I, II, III*: 30 min. after intracisternal injection; exposure, 32 hr. *D I, II, III*: corresponding sections of a formaldehyde-fixed brain.

the injection. By that time the isotope was found throughout the entire brain, with the exception of the frontal lobes, cranially, and the spinal cord, caudally, where the cerebrospinal fluid flow was not yet able to carry the bulk of the injected solution. Radioactive phosphorus was being absorbed and incorporated with great rapidity,

and large areas of the brain were almost saturated within the first 10 min. after the injection (Fig. 2*B*). Obviously, the places showing the highest activity were those surrounded by cerebrospinal fluid spaces and near the cisterna magna—the medulla oblongata, the cerebellum, the pons, the mesencephalon, and the corpora quadrigemina. These areas were practically saturated within one hour of the injection and contained a high amount of P^{32} in their superficial, as well as in their deep, layers. P^{32} penetrated the brain stem with equal speed from the cisterna venae magnae cerebri (ambiens), outside, and from the aqueduct, inside (Fig. 3*II*). The isotope similarly invaded the cerebral hemispheres from two directions, from the subarachnoid space and basal cisterns, on the one side, and from the ventricular system, on the other. Although these two gateways of absorption could be recognized in all the experiments, their importance in a given case depended largely upon the tech-

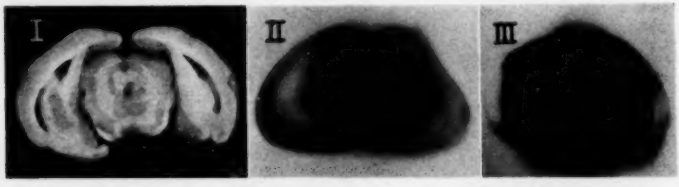

Fig. 3.—Radioautographs of the cross section of the occipital lobes and of the midbrain, 10 min. (*II*), and 60 min. (*III*), after intracisternal injection of P^{32}; exposure, 45 hr.

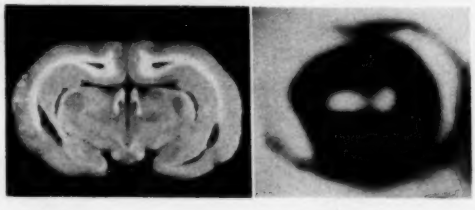

Fig. 4.—Radioautograph of a cross section of the brain one hour after cisternal administration of P^{32}; exposure, 45 hr.

nique of the injection. When the volume of cerebrospinal fluid withdrawn was exchanged for the same amount of P^{32} solution, there was usually a good deal of back flow of the isotope into the ventricles via the foramens of Luschka; consequently, considerable absorption of phosphorus by the brain took place through the walls of the ventricles (Fig. 2*B*). On the other hand, when cerebrospinal fluid was removed in a slight excess, there was more absorption into the cortex of the brain from the subarachnoid spaces. In most experiments the basal cisterns supplied the brain with more P^{32} than did the space over the convexity (Fig. 2*C*). An interesting and constant finding was that after 10 to 30 min. the cerebral cortex lost some of its radioactivity, later becoming much poorer in P^{32} than the underlying parts of the cerebral hemispheres (Figs. 3*III* and 4). The frontal lobes continued to have a lower radioactivity for several hours after the injection. The P^{32} content

of the lower thoracic portion of the spinal cord remained exceedingly low—as late as four hours afterwards—the time of the longest experiment in which the spinal cord was examined.

The pituitary gland contained less P^{32} after cisternal than after intravenous administration, despite the fact that a large part of the isotope adhering to its surface certainly could not be satisfactorily rinsed off. There was about one-half to one-third as much radioactive phosphorus in the pituitary after cisternal injection as after intravenous administration. The ratio of P^{32} in the pituitary to that in the white matter of the brain was about 1:3 to 1:4 with intracisternal injection as compared with 50:1 to 60:1 with intravenous injection (Fig. 1*A* and *B*).

The table shows the P^{32} content of various parts of the central nervous system in different experiments.

Radioactive-Phosphorus (P^{32}) Content of Various Parts of the Central Nervous System *

	P^{32} Given Intravenously	P^{32} Given Intracisternally		
Amount of P^{32}, μc/kg. body wt.	20	1	1	1
Duration of experiment	24 hr.	10 min.	30 min.	60 min.
Frontal lobes				
Cortex	2.0	6.0	11.0	36.0-100.0
White matter	1.0	4.0	4.0	32.0
Cerebral hemispheres				
Cortex of convexity	2.5	30.0	9.0-22.0-39.0	8.0-13.0
Basal cortex	3.5	38.0	80.0	260.0
Central substance	1.3	2.0-4.0	25.0	195.0
Lateral and third ventricles				
(Choroid plexus and walls)	4.5-9.0	95.0	90.0	88.0
Aqueduct	6.4	122.0	95.0	430.0
Mesencephalon				
Surface	2.5	199.0	200.0	43.0
Depth	2.0	15.0	38.0	63.0
Pons	2.0	88.0	100.0	124.0
Fourth ventricle				
(Choroid plexus and walls)	9.4	199.0	172.0	185.0
Cerebellum				
Cortex	4.0	30.0	52.0	42.0
White matter	1.5	12.0	28.0	40.0
Medulla	4.4	137.0	126.0	80.0
Spinal cord (thoracic)	3.0	1.0	3.0	6.0
Pituitary gland	85.0	12.0	33.0	69.0

* Values are expressed in counts per minute per milligram of tissue.

COMMENT

Numerous previous experiments had shown that many of the vital dyes, when injected intravenously in animals, do not cross the blood-brain barrier, that the stained areas of the brain are pretty well limited to the walls of the blood vessels, the choroid plexus, the pineal body, and the pituitary gland, and that there was usually a faint coloration of the hypothalamus around the infundibulum. Injected directly into the cerebrospinal fluid, the same dyes cause intensive discoloration of the whole central nervous system except the areas described above. It is also known that there is no defined cerebrospinal fluid-brain barrier. The diffusion of a vital dye from the cerebrospinal fluid into the brain is determined mostly by its electrochemical properties and by the size of its particles. Spatz [7] demonstrated that dyes of small

7. Spatz, H.: Die Bedeutung der vitalen Färbung für die Lehre vom Stoffaustausch zwischen dem Zentralnervensystem und dem übrigen Körper, Arch. Psychiat. **101**:267-305, 1933.

molecular weight diffuse from the cerebrospinal fluid to various depths in the nervous tissue, obeying rules similar to those of diffusion of a substance from water to a gel. In previous animal experiments in which vital dyes of determined particle size were used, I found that the dyes penetrated the brain from the cerebrospinal fluid if their particle radius was less than 10 A.; the thickness of the dyed layer was related primarily to the size of the particles.[8]

The main criticism directed against such investigations was the unphysiological aspect of the experiments in introducing such substances into the delicately balanced internal milieu of the brain. This aspect is well illustrated by the toxic effect of the dyes on the nervous system. Another objection was that the findings were purely qualitative—that no attempt was made to take into consideration the difference between the amount of plasma and that of cerebrospinal fluid.

Borell and Örström,[6] injecting P^{32} in rabbits intraperitoneally, found a very low radioactivity in the brain except for the pineal gland, the pituitary, the choroid plexus, and parts of the hypothalamus, which revealed high specific activity. Soon afterward Lindberg and I[2] demonstrated that these portions differ fundamentally from other parts of the brain and that it is the manner of its introduction—intracisternal or intravenous—that determines the accumulation of P^{32} in the various intracranial structures. We also found 20% of the cisternally administered P^{32} inside the brain 30 min. after the injection, about a quarter of it being already in organic compounds. Lindberg and Ernster[3] carried out similar experiments in rats, finding an even higher deposit of P^{32}, chiefly in the form of adenosinetriphosphate and phosphocreatine. Sacks and Culbreth,[4] in a series of experiments on cats, also found a rapid interchange of phosphate between the cerebrospinal fluid and the brain substance, with a high rate of incorporation of the tracer into the phosphocreatine and labile phosphorus of the adenosinetriphosphate of the brain.

The high P^{32} content of the pituitary gland after intravenous injection of the tracer can be explained by the lack of any particular barrier in that area and by a vigorous metabolism. It is nevertheless interesting that this gland absorbs relatively less phosphorus from the cerebrospinal fluid. This finding is in accord with vital-dye studies. I was unable, however, to demonstrate any appreciable difference in behavior between the vegetative centers of the hypothalamus and the rest of the central nervous system. Our present method of measuring radioactivity in microscopic sections of the brain may not be refined enough for that purpose. There are indirect indications that the blood-brain barrier is more permeable in the hypothalamic nuclei, as indicated by the strong circulatory resistance of the supraoptic and paraventricular nuclei (Grenell and Kabat[9]) and by the observations of Borell and Örström,[6] who found after intravenous injection of P^{32} an area of high activity in this region.

Our experiments show that the decisive factor of the penetration of radioactive phosphorus into the central nervous system is the concentration of the isotope in the cerebrospinal fluid space nearest the respective area. The absorption takes place

8. Unpublished data.

9. Grenell, R. G., and Kabat, H.: Central Nervous System Resistance: II. Lack of Correlation Between Vascularity and Resistance to Circulatory Arrest in Hypothalamic Nuclei, J. Neuropath. & Exper Neurol. **6**:35-43, 1947.

in a short time; the rapidity with which phosphorus is carried into the depths of the brain is impressive. There is no basic difference between the penetration through the pia-covered cortex and the ependyma-lined ventricular wall. It is strange that the activity is lower in the cortex than in the underlying structures, a finding at first thought due to the rinsing of the brain, which removes not only the radioactive cerebrospinal fluid but also much of the radioactivity of the cortex. The same observation has been made, however, in experiments in which the brain was hardly rinsed at all. I am inclined to think that it represents a physiological phenomenon of white matter binding more phosphorus.

These data show that one hour after injection into the cistern P^{32} is distributed all over the brain, although it is not yet evenly mixed in the whole cerebrospinal fluid, especially not in the spinal fluid.

If it is assumed that a valid comparison can be made of the P^{32} contents of the brain at the height of concentration following intravenous injection and cisternal administration, respectively, the ratio of the former to the latter is 1:20 to 1:50, with some local variations. The central nervous system binds phosphorus eagerly—as a matter of fact, so eagerly that the almost impermeable blood-brain barrier is necessary to protect it from an overabundance of phosphorus, since the nerve tissue itself does not seem to possess such a regulatory system. The barrier is more permeable for dyes and pigments in young animals, and it is probably the same for phosphorus. That would explain the observations of Fries, Changus, and Chaikoff,[10] who found the highest phospholipid activity in the central nervous system of rats on the day of birth, as measured by parenterally-given P^{32}. From birth until the time the rat attains a weight of 50 gm., a precipitous decline in phospholipid activity occurs through the entire central nervous system.

The effect of the blood-brain barrier is twofold: It slows down the absorption by the brain of phosphorus from the blood and supplies the central nervous system with a relatively small amount of it. The striking difference between the central nervous system and other "nonprotected" organs is well illustrated by the behavior of the pituitary gland. It is probably more than a coincidence that our ratio of counts is similar to the one Selverstone, Sweet, and others[11] found for the P^{32} content of the normal human brain and brain tumors.

At present it cannot be said with certainty how much of the P^{32} found in the brain after intravenous administration passed the blood-brain barrier directly and how much of it was absorbed from the cerebrospinal fluid after entering the latter through the blood-cerebrospinal fluid barrier (choroid plexus). According to Sacks and Culbreth[4] the intravenously injected tracer becomes available to the brain substance for turnover by secretion into the cerebrospinal fluid.

10. Fries, B. A.; Changus, G. W., and Chaikoff, I. L.: Radioactive Phosphorus as an Indicator of Phospholipid Metabolism: IX. Influence of Age on the Phospholipid Metabolism of Various Parts of the Central Nervous System of the Rat, J. Biol. Chem. **132**:23-34, 1940. Fries, B. A., and Chaikoff, I. L.: The Phosphorus Metabolism of the Brain as Measured with Radioactive Phosphorus, ibid. **141**:479-485, 1941.

11. Selverstone, B.; Solomon, A. K., and Sweet, W. H.: Location of Brain Tumors by Means of Radioactive Phosphorus, J. A. M. A. **140**:277-278 (May 21) 1949. Selverstone, B.; Sweet, W. H., and Robinson, C. V.: The Clinical Use of Radioactive Phosphorus in the Surgery of Brain Tumors, Ann. Surg. **130**:643-651, 1949.

SUMMARY

Radioactive phosphorus was given to one group of rabbits intravenously in the amount of 20 μc per kilogram of body weight, and intracisternally to another group in the amount of 1 μc per kilogram of body weight. The animals were killed from 10 min. to 24 hr. after the injections, and the P^{32} content of various parts of the central nervous system was determined.

A maximum concentration of the isotope was reached in the brain 12 to 24 hr. after intravenous injection and 30 to 60 min. after intracisternal administration. After its injection into the cistern, P^{32} penetrated the cortex and the lining of the ventricles with equal rapidity and accumulated in the brain substance to its entire depth.

The P^{32} deposit in the brain, as compared at the times of maximum concentration, was 20 to 50 times as high after intracisternal as after intravenous administration.

More P^{32} concentrated in the pituitary gland after intravenous than after intracisternal injection.

The role played by the blood-brain and blood-cerebrospinal fluid barriers in the distribution of phosphorus is discussed.

CYTOLOGY OF RABBIT NEURONS AFTER "MALONONITRILE" ADMINISTRATION

CHAN-NAO LIU, Ph.D.
PHILADELPHIA

CHROMATOLYSIS of the basophilic Nissl substance of the cytoplasm of neurons is a well-recognized phenomenon that occurs when the axon is severed. The pattern of this chromophil material undergoes alterations when the neuron is injured in other ways. It can be influenced to a certain extent by anoxia and by concussion, and it begins to change promptly after death. Many investigators have held that alterations in amount and arrangement of the Nissl substance reflect changes in the metabolic state of the neuron. The theory that intense functional excitation of a neuron leads to depletion of the Nissl substance has attracted many. Dolley [1] was among the first to deal extensively with this problem, but his results, which appeared to support the theory, were discredited to a large extent by later investigators. More recently, Hydén [2] reported that electrical excitation of neurons for only five minutes increased the nucleotide and protein content of the cytoplasm and that periods of stimulation of 10 min. or more exhausted these substances and produced a picture of chromatolysis. After repeating and extending Hydén's experiments, my associates and I [3] failed to elicit any demonstrable cytological changes in the Nissl substance of neuron cytoplasm after intense electrical excitation.

Much interest has been elicited by other experiments, reported by Hydén and Hartelius,[4] in which a chemical agent, "malononitrile," was injected intravenously into rabbits, with the apparent result that the large neurons of the central nervous system displayed an increase in the amount of basophilic cytoplasmic material. It was claimed that a marked increase in the ribose polynucleotide and protein contents of the cytoplasm could be demonstrated one hour after administration of the drug and that the effects persisted as long as 48 hr. Hydén and Hartelius attempted to

From the Department of Anatomy, University of Pennsylvania School of Medicine.

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1. Dolley, D. H.: The Morphology of Functional Depression in Nerve Cells and Its Significance for the Normal and Abnormal Physiology of the Cell, J. M. Res. **29**:65-129 (Aug.) 1913.

2. Hydén, H.: Protein Metabolism in the Nerve Cell During Growth and Function, Acta physiol. scandinav. (Supp. 17) **6**:88-97, 1943.

3. Liu, C.; Bailey, H. L., and Windle, W. F.: An Attempt to Produce Structural Changes in Nerve Cells by Intense Functional Excitation Induced Electrically, J. Comp. Neurol. **92**:169-182 (April) 1950.

4. Hydén, H., and Hartelius, H.: Stimulation of the Nucleoprotein-Production in the Nerve Cells by Malononitrile and Its Effect on Psychic Functions in Mental Disorders, Acta psychiat. et neurol. (Supp.) **48**:1-117, 1948.

correlate their experimental observations with studies of patients with mental disorders. The nerve cells of the brains of such patients appeared to the investigators to be deficient in the basophilic cytoplasmic substance and resembled chromatolytic nerve cells that Hydén had seen in his animals after electrical stimulation. It was reasoned that "malononitrile" might be capable of restoring exhausted neurons to their normal functional state. They proceeded to administer the drug to patients with severe mental disturbances and declared that a few appeared benefited by the treatment.

The encouraging observations of Hydén and Hartelius have led other investigators to employ "malononitrile" to stimulate nucleotide production in exhausted nerve cells. Szanto and Felsenfeld [5] reported that "malononitrile" prolonged the survival time of mice that had been infected with the Lansing strain of poliomyelitis virus but that the effect persisted only as long as the drug was given. Milzer and Adelman [6] were unable to observe any beneficial effect of administering "malononitrile" to mice infected with this virus. Neither group of investigators carried out histological studies. Recently, two clinical studies have been reported. One group of investigators [7] was unable to observe beneficial results of "malononitrile" administration; the other group [8] reported equivocal results.

Since we had been unable to bring about any appreciable change in the amount or arrangement of the basophilic Nissl substance of neurons by intense functional stimulation induced electrically for either brief or prolonged periods, it was decided to try "malononitrile" experimentally. If "malononitrile" could be used to stimulate rapid production of nucleotides and proteins in neurons, it would provide a valuable tool for further cytochemical studies of the nervous system.

MATERIAL AND METHODS

Eight young adult male and female rabbits received injections of a solution of "malononitrile" [9] in doses of 4.1 to 7 mg. per kilogram of body weight, as recommended by Hydén and Hartelius. An equal number of similar animals receiving no drug served as controls. The animals were allowed to live one to two hours after the injection. Three methods were employed for obtaining nerve tissue for histological study: (*a*) Biopsies were performed with the animal under pentobarbital anesthesia, (*b*) animals were killed by air embolism, or (*c*) animals were killed by the perfusion-fixation technique with a solution of formaldehyde U. S. P. (1:10)-gum acacia solution.[10] Tissues from representative parts of the central nervous system of the biopsied and the embolized animals were removed and fixed immediately by immersion in Carnoy's solution or in solution of formaldehyde U. S. P. 1:10 saturated with mercury bichloride. Tissues from the perfused animals were preserved in solution of formaldehyde U. S. P. (1:10). Paraffin sections 5μ thick were mounted on quartz slides for photomicrography with an ultraviolet microscope equipped with Zeiss quartz monochromatic objectives and a light source

5. Szanto, P. B., and Felsenfeld, O.: Influence of Malononitrile upon Poliomyelitis in Mice, Proc. Soc. Exper. Biol. & Med. **72**:15-17 (Oct.) 1949.

6. Milzer, A., and Adelman, P.: Failure of Malononitrile in Therapy of Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **74**:134-135 (May) 1950.

7. MacKinnon, I.; Hoch, P.; Crammer, L., and Waelsch, H.: Use of Malononitrile in the Treatment of Mental Illnesses, Am. J. Psychiat. **105**:686-688 (March) 1949.

8. Meyers, D.; Shoemaker, T. E.; Adamson, W. C., and Sussman, L.: Effect of "Malononitrile" on Physical and Mental Status of Schizophrenic Patients, Arch. Neurol. & Psychiat. **63**:586-592 (April) 1950.

9. The source of drug was Bios Laboratory, New York.

10. Koenig, H.; Groat, R. A., and Windle, W. F.: A Physiological Approach to Perfusion-Fixation of Tissues with Formalin, Stain Technol. **20**:13-22 (Jan.) 1945.

emitting at 2,537 A. Similar sections cut at 10μ were mounted on glass slides for staining by the buffered thionine technique[11] at a pH of 4.5 or by the Feulgen method. Further to assure fair comparison of material from experimental animals with that from controls, sections of both were stained simultaneously in the same staining dishes.

RESULTS

The behavior of experimental animals after administration of "malononitrile" resembled that described by Heymans and Masoin[12] and Hydén and Hartelius.[4] Vasodilatation of the blood vessels of the ears was observed within 15 to 20 min. and persisted for periods of 10 to 20 min. There were a slight increase in rate of respiration and an increase in movements of chewing, perhaps due to excessive salivation. Some of the animals exhibited a decrease in rectal temperature, amounting to as much as 3 degrees (F.). All showed hypalgesia an hour after injection. It was apparent from these observations that the "malononitrile" employed in the present experiments produced physiological changes comparable with those elicited by the drug used by previous investigators.

The results of the histological studies can be summarized in few words. Central nervous tissue from the animals that had been fixed by the perfusion method revealed consistent uniformity of neuron staining with thionine. The chromophil substance of the neuron cytoplasm was no different in the animals that had received "malononitrile" than in those that served as controls. Sections from the experimental and control animals were indistinguishable from one another. The Feulgen stain revealed no difference. Similarly, the photographic records made with the ultraviolet microscope, employing thin unstained sections of spinal ganglia and spinal cord, as well as various portions of the brain, revealed no difference at all between the experimental and the control animals in respect to ribose-nucleotide absorption at 2,537 A.

Sections cut from pieces of nerve tissue fixed by immersion in Carnoy's fluid or in the formaldehyde-mercury bichloride fluid revealed no difference between the experimental and the control animals. However, the tissue fixed by immersion differed considerably in cytological appearance from that fixed by perfusion. Occasional darkly stained and shrunken nerve cells were observed in all parts of the nervous system after immersion fixation. These hyperchromatic neurons were as numerous in the material from control animals, which had received no drug, as they were in the materials from the animals receiving injections of "malononitrile."

COMMENT AND CONCLUSIONS

Since the physiological and toxic reactions of animals treated with "malononitrile" appeared to be similar in the present experiments to those reported by Hydén and Hartelius,[4] and since the doses of this chemical agent which were employed were comparable in the two groups of experiments, it is unlikely that the pronounced differences in the cytological observations were referable to differences in the drug or in its administration. Perhaps the present failure to detect any structural change following administration of "malononitrile" to the rabbit, in contrast to the marked structural changes reported by Hydén and Hartelius, is related to differences in histological techniques and methods of preparation of the tissues. The tissues from

11. Windle, W. F.; Rhines, R., and Rankin, J.: A Nissl Method Using Buffered Solution of Thionin, Stain Technol. **18**:77-86 (April) 1943.

12. Heymans, J., and Masoin, P.: Étude physiologique sur les dinitriles normaux, Arch. internat. pharmacodyn. **3**:77, 1897.

experimental animals studied by Hydén and Hartelius were not prepared by the perfusion-fixation technique, but were fixed by immersion in Carnoy's or in the formaldehyde-mercury bichloride fixing fluid. It has been maintained by Windle and associates that one cannot prevent the appearance of hyperchromatic neurons in histological sections when immersion-fixation techniques are used, even when very small pieces of brain substance are immersed in fixing fluid immediately after death. The present observations confirm this.

In view of the present failure to confirm the observations of Hydén and Hartelius, and in view of the knowledge that neurons of the central nervous system undergo pronounced changes soon after death [13] and that immersion fixation results in the appearance of many hyperchromatic cells, it is suggested that future experiments of this type be subjected to more critical cytological controls than have commonly been used in the past.

Unless future studies reveal more subtle changes than can be demonstrated by the techniques employed in the present experiments, it is unreasonable to expect the chemical agent, "malononitrile," to increase significantly the nucleotide and protein content of the cytoplasm of neurons of the central nervous system. The concept of rapid depletion of these substances in the cytoplasm during intense functional stimulation and the rapid replacement under the influence of such a drug as "malononitrile," as described by Hydén, is one that cannot be supported by the controlled cytological experiments of this laboratory.

SUMMARY

Experiments were performed on rabbits to determine the effect of "malononitrile" on nerve cells. Histological comparison of control and experimental animals failed to reveal any changes in Nissl pattern of neurons of the spinal ganglia, spinal cord, and various parts of the brain after administration of "malononitrile" when adequate precaution against postmortem and fixation artefacts was observed. No change could be detected by ultraviolet photomicrography at a wave length of 2,537 A.

13. Koenig, R.: Post-Mortem Changes Within the Central Nervous System, Anat. Rec. **103**:477 (March) 1949.

COMPARATIVE PSYCHOLOGICAL STUDY OF HYPERKINETIC AND AKINETIC EXTRAPYRAMIDAL DISORDERS

V. A. KRAL, M.D.
AND
HERBERT DÖRKEN Jr., Ph.D.
MONTREAL, CANADA

ALTHOUGH there is a considerable number of reports on record of psychopathological changes of various kinds in cases of circumscribed lesions of the subcortical gray structures of the brain, systematic psychological investigation of such cases has been performed only rarely. This may be due partly to peculiarities in the symptoms and course of the illness in such cases, partly to the fact that the underlying anatomical lesion has been found, in some cases, only unexpectedly at autopsy [1] but mainly to the tendency of the majority of Rorschach investigators to formulate a theory of "generalization" in regard to the influence of organic brain damage. There has been a tendency in these psychological investigations to consider the different cases and various kinds of organic brain damage as though they formed a single entity in the psychological respect. It could be shown, however, that this generalizing view should be modified, at least to a certain extent.[2]

In remarkable contrast to the scarcity of psychological investigations in cases of circumscribed localized lesions of the brain stem, there exists a considerable number of reports of psychological investigations of a disease which in its chronic state affects mainly subcortical structures of the brain, namely, postencephalitic Parkinsonism.[3] This difference is probably due to the higher incidence of such cases, their usually long observation period, and the social implications of this condition. However, these investigations have been performed, not with regard to the particular localization of the underlying brain lesion, but, rather, to characterize in so far as possible the psychological aspect of this disease entity.

From Verdun Protestant Hospital.

1. Stern, K., and Dancey, T.: Glioma of the Diencephalon in a Manic Patient, Am. J. Psychiat. **98**:716-719, 1942. Guttmann, E., and Hermann, K.: Über psychische Störungen bei Hirnstammerkrankungen und das Automatosesyndrom, Ztschr. ges. Neurol. u. Psychiat. **140**:439-472, 1932.

2. Kral, V. A., and Dörken, H., Jr.: Influence of Subcortical (Diencephalic) Brain Lesions on Emotionality as Reflected in the Rorschach Color Responses, Am. J. Psychiat. **107**:839-843, 1951.

3. (*a*) Shaskan, D.; Alper, K., and Yarnell, H.: Physical, Psychiatric and Psychometric Studies on Postencephalitic Parkinsonism, Arch. Neurol. & Psychiat. **48**:666-668, (Oct.) 1942. (*b*) Veit, H.: Der Parkinsonismus nach Encephalitis epidemica im Rorschachschen Formdeutversuch, Ztschr. ges. Neurol. u. Psychiat. **110**:301-324, 1927. (*c*) Endacott, J.: The Rorschach Test in Post-Encephalitis, Illinois M. J. **88**:256-258, 1945. (*d*) Steck, H.: Les syndromes mentaux postencéphalitiques, Schweiz. Arch. Neurol. u. Psychiat. **27**:137-173, 1931.

PRESENT INVESTIGATION

Material.—The purpose of the present communication is to present the results of psychological tests in cases of extrapyramidal diseases, both of the akinetic and of the hyperkinetic type. While the first group contains six cases of postencephalitic Parkinsonism, these were chosen not with regard to the disease entity itself, but in accordance with the accepted view that the characteristic neurological symptomatology is caused by lesions of the pallidum-substantia nigra system. Therefore, cases presenting the Parkinson syndrome of other than encephalitic origin (arteriosclerotic and degenerative) were also included in this group. The psychological results obtained will be compared with those in a second group of cases, which neurologically were characterized by an extrapyramidal hyperkinesis. The latter group was also composed of cases of diseases of various origins, their common feature being the neurological symptoms pointing to localization of the underlying changes in the striate body.[4] Wilson,[5] however, has stressed the role of cortical involvement in senile and Huntington's chorea, and, according to modern views, the lesion underlying the hyperkinetic phenomena interrupts a corticostriate inhibitory circuit.[6]

The majority of patients in both groups had been committed to a psychiatric hospital.[7] They therefore showed differing psychiatric symptoms which may or may not be related to the neurological symptoms, a point which will be referred to later. However, it should be mentioned that no selective principle other than the neurological symptomatology was involved in the collection of our case material.

Exclusive of two cases to be used for illustrative discussion, there were 10 subjects in each group. The ages of the hyperkinetic patients ranged from 17 to 79, with a mean of 54.9; the ages of the akinetic patients, from 36 to 73, with a mean of 52.1. Thus, the ages were comparable, though the hyperkinetic group included one subject under 36 yr. of age.

The intelligence, as measured by the Wechsler-Bellevue Adult Intelligence Scale,[8] showed a considerable difference in the two groups. The intelligence quotients of the hyperkinetic subjects ranged from 48 to 77 (mental deficiency to borderline defective intelligence), with a mean of 66.0, whereas those of the akinetic patients ranged from 66 to 123 (borderline defective to superior intelligence), with a mean of 104.3. At least for our present cases, the damage to the brain among the hyperkinetic subjects was, therefore, accompanied by a more pronounced intellectual impairment.

All subjects were well able to distinguish and identify the primary colors. No evidence of color blindness could be detected.

Results.—The results of the Rorschach test (mean values) are presented in detail in Table 1. It may readily be seen that both groups deviate, on the average, to a striking degree from the norm. In particular, the deviations common to the two groups are as follows:

1. The extreme limitation of productivity (mean R = 10.3 and 9.8). The number of responses normally range from 20 to 40.[9]

2. The high number of rejections. Normal subjects seldom reject a card.

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4. Brock, S.: The Basis of Clinical Neurology, Baltimore, Williams & Wilkins Company, 1945.

5. Wilson, S. A. K.: Neurology, London, Edward Arnold & Co., 1940.

6. Monnier, M.: L'organisation des fonctions motrices: III. Physiologie de l'appareli dit extrapyramidal, Schweiz. Arch. Neurol. u. Psychiat. **62**:151-198, 1948.

7. Dr. N. Viner, associate in neurology, Montreal General Hospital, extended us the opportunity of examining four patients with Parkinsonism at the neurological outdoor clinic of this hospital.

8. Wechsler, D.: Measurement of Adult Intelligence, Ed. 3, Baltimore, Williams & Wilkins Company, 1944.

9. Klopfer, B., and Kelley, D.: The Rorschach Technique, Yonkers-on-Hudson, N. Y., World Book Company, 1942, p. 208.

3. The few M (human movement) and FC (form-color) responses, the presence of which is generally interpreted as indicative of creative ideation (inner, or fantasy, life) and socially adapted emotional expression, respectively.

4. The narrowing of the range of the thought content, described as stereotypy and reflected by the high percentage of A (animal) responses.

5. The meagerness or meager use of intellectual capacities, as indicated by the low formal accuracy of perception, that is, form level of response [10] (both total and average).

6. The narrowing of the personality resources, as seen in the predominant use of pure form responses and consequent sharp restriction (generally absence) of those determinants which reflect sensitivity, anxiety, or conflict.

7. The extreme scarcity of good original responses (O +).

It must be emphasized, however, that these features are deviant from the normal, not in the sense that there is positive expression of psychopathology, but,

TABLE 1.—*Rorschach Test Results for the Hyperkinetic and the Akinetic Group**

	M	FM	m	k	K	FK	F	Fc	c	C'	FC	CF	C	R	Rejections
Hyperkinetic	0.4	1.8	...	...	...	...	5.6	...	0.1	0.5	0.5	0.4	1.0	10.3	1.8
Akinetic	0.9	3.1	...	0.1	...	...	4.4	0.6	0.1	...	0.3	0.3	...	9.8	2.6

	F%	F-%	Ster.† A%	W%	D%	d%	Dd8%	O%	O+%	Av. R.T.‡	Piotrowski's Sign	Ross Instability	Ross Disability	Form Level Total	Form Level Av.
Hyperkinetic	54.8	22.0	55.2	45.8	44.1	1.2	8.6	10.4	4.7	7.7	5.1	9.8	21.9	4.8	0.6
Akinetic	46.5	17.4	67.4	53.9	34.7	7.3	4.1	5.1	3.7	41.2	2.3	20.2	10.3	8.9	0.8

No. of Cases	Hyperkinetic	Akinetic
M + FM + m = 0	1	1
k + K + FK = 0	10	9
FC + CF + C = 0	1	7

* Each group contained 10 subjects.
† "Ster." indicates stereotypy.
‡ "Av. R. T." means average reaction time, in seconds.

rather, in that certain usual aspects of personality are absent. The absence of these features may be likened to "negative symptoms" in the sense of Jackson.[11]

Evidence of positive psychopathological test signs is also present. Inferior or inaccurate responses (F —, O —, etc.) should not be present in the normal record; their presence speaks for lack of critical control or inhibition. A considerable number of the responses of our patients were grossly inaccurate (F —), indicating an inadequate ability to screen and select the more appropriate of those associations generated by the stimulus.

Two types of formal inaccuracy must, however, be distinguished. One is based on a perceptual distortion; the other stems from concept-determined responses. In perceptual distortion the patient may give a seemingly adequate response (perhaps common or popular), but yet not be able to locate his percept accurately on the blot. (Such patients usually express concern over their performance—

10. Klopfer, B., and Davidson, H.: The Rorschach Technique, Yonkers-on-Hudson, N. Y., World Book Company, 1946.

11. Fulton, J.: Physiology of the Nervous System, New York, Oxford University Press, 1938.

perplexity [12]—and are the less severely impaired.) This cannot be considered as basically an expressive phenomenon. "Concept-determined" responses, on the other hand, that is, responses which are inaccurate in the sense that they bear no essential or adequate formal relation to the blot, are based on a lack of critical control or inhibition, and are determined largely by the patient's associational content at the time of examination, rather than by the actual qualities of the stimulus (ink blot).[13] They may be regarded as the Rorschach equivalent of "release phenomena." [11] Though these concept-determined responses may be random or changing, the process of perseveration is frequently found. Related is the sign of automatic phrasing.[14]

Many responses, while not strictly inaccurate, were exceedingly vague and poorly organized (high W%, largely Wv). These were also responses given without adequate critical selection or control.

It must be emphasized that it is not the total number of Rorschach responses that is increased by the release phenomena, but, rather, the pathological or defective ones that are in excessive evidence. Probably, the impairment of abstraction [15] results in the lower total number of responses (R). The patient with an organic lesion tends to "name" the blots rapidly and inaccurately, and thus does not appreciate the possibility of varying interpretations from which normal productivity is derived.

At times, the rapidity of delivery and/or poor organization made it seem as though these responses were reflex-like, or automatic. Of the various groups of patients with localized brain lesions whom we have investigated, this has been observed as particularly characteristic of patients with hyperkinesis.

The rapid tempo of response is generally absent in patients with Parkinsonism, and the Rorschach equivalent of release phenomena least clearly observable. Here, with slowing of the thought processes (bradyphrenia), the phenomena of formal inaccuracy are less apparent as resulting from an actual mechanism of release.

A further illustration of "automatic" response is seen in the crude (pure) color responses, particularly color naming, which were found in the records of patients in our hyperkinetic (and cortical [16]) group.

In that the records of our patients generally contained few responses, poor formal accuracy, frequent rejections, diminished M responses, and such signs as

12. Piotrowski, Z.: The Rorschach Inkblot Method in Organic Disturbances of the Central Nervous System, J. Nerv. & Ment. Dis. **86**:525-537, 1937.

13. Levine and associates report that blot-determined responses are characteristic of the graphic Rorschach response of patients with organic disease of the brain (Levine K., and Grassi, J.: The Relation Between Blot and Concept in Graphic Rorschach Responses, Ror. Res. Exch. **6**:71-73, 1942. Rochlin, G., and Levine, K.: The Graphic Rorschach Test, Arch. Neurol. & Psychiat. **47**:438-448 [March] 1942). This is actually not a contradiction in findings. Just as such a patient is prone, in responding verbally, to name blots in accordance with his associations, rather than to point out the formal qualities of the blot; so, too, when asked to draw his concepts, he is prone to make an exact representation of the blot without regard to his concept. Thus, both the verbal and the graphic responses demonstrate the "concrete" approach of a patient with organic disease who has suffered loss of the capacity for abstraction.

14. Klopfer and Kelley,[9] p. 334.

15. Kelley, D.: The Rorschach Method as a Means for the Determination of the Impairment of Abstract Behavior, Rorschach Res. Exch. **5**:85-88, 1941.

16. The results obtained with our cortical group are to be presented in another paper.

perseveration, impotence, perplexity, and automatic phrasing, they are in agreement with the findings of Piotrowski [17] and Schenk.[18] These have been considered features common to the records of subjects with intracranial organic disease.[19]

The results presented in Table 1 indicate that the test responses of patients with hyperkinetic and of patients with akinetic types of extrapyramidal lesions show not only common features, but also several striking differences from one another. The reaction times of the hyperkinetic group were unusually fast, almost automatic; those of the Parkinsonian patient, on the other hand, frequently displayed the classic bradyphrenia. As might be expected, the latter also showed the highest degree of stereotypy.

It was only the akinetic group that did not reach the expected criterion when the well-known organic ratings of Piotrowski [20] or Ross [21] were applied. But one patient with Parkinsonism gave a "positive organic rating" according to Piotrowski's signs; the same patient (the only one of this group of below-average intelligence) also showed a higher "disability" rating, according to Ross's method. The other patients, however, with the exception of one within the normal range, were strongly weighted to the "instability" or "neurotic" side of Ross's ratio. This unusual finding was noted, in essence, by Endacott,[3c] who referred to the thesis of Jelliffe that the postencephalitic patient has two threats: a real one, caused by the disease, and a neurotic one, caused by reactivation of old impulses and conflicts which break out of repression because of damage to the nervous system.

Except in some cases of Parkinsonism with clinical signs of involvement of the diencephalon,[2] color response is preserved. This distinction may perhaps serve as one of the finer differentiating signs of the extent of the lesion in Parkinsonism. Color naming, an indication of emotional confusion and/or deterioration,[22] was present in four cases of hyperkinesis, and appears dependent on a significant intellectual defect.

While not included in the statistical evaluation, a further case of Parkinsonism is of particular interest. The patient was of above average intelligence and, from the responses given to the first seven Rorschach cards, displayed the "typical" stereotypy, long reaction time, and "neurotic," rather than "organic," ratings. The record could not be completed, as presentation of Card VIII (multicolored

17. Piotrowski, Z.: On the Rorschach Method and Its Application in Organic Disturbances of the Central Nervous System, Rorschach Res. Exch. **1**:23-29, 1936; footnote 12.

18. Schenk, V.: Der Formdeutversuch (Rorschach) bei organischen Hirnerkrankungen, Psychiat. en neurol. bl. **42**:350-372, 1938.

19. While more typical of such conditions, these features may be found in other psychiatric disorders (Lynn, J.; Levine, K., and Hewson, L.: Psychologic Test for the Clinical Evaluation of Late "Diffuse Organic," "Neurotic," and "Normal" Reactions After Closed Head Injury, A. Res. Nerv. & Ment. Dis., Proc. [1943] **24**:341-346, 1945). For example, 45% of a control group of schizophrenic patients (Dörken, H., Jr., and Kral, V. A.: The Psychological Differentiation of Organic Brain Lesions and Their Localization by Means of the Rorschach Test, read before the annual meeting of the American Psychiatric Association, Cincinnati, 1951) demonstrated a positive organic rating in accordance with the criteria of Piotrowski.[12]

20. Piotrowski, Z.: Positive and Negative Rorschach Organic Reactions, Ror. Res. Exch. **4**:147-151, 1940; footnote 17.

21. Ross, D.: A Quantitative Use of the Rorschach Method, Am. J. Psychiat. **101**:100-104, 1944; Some Rorschach Ratings of Clinical Value, Ror. Res. Exch. **8**:1-9, 1944.

22. Piotrowski.[12] Kisker, G.: Rorschach Analysis of Psychotics Subjected to Neurosurgical Interruption of the Thalamo-Cortical Projections, Psychiatric Quart. **18**:43-52, 1944.

card, following four achromatic ones) precipitated an oculogyric crisis. Though the patient had given an excellent color response to Card II, he explained this phenomenon as follows: "My eyes go up, and they won't come down; it's from seeing all the color—hasn't happened in a long time. To play cards bothers me; black and red on the cards bothers me, especially the face cards." Endacott [3c] noted that tremor often became more pronounced on response to the colored blots.

Our observation, as well as Endacott's, therefore points to the close relation of emotional and so-called neurotic symptoms with oculogyric crises, as noted by Stern,[23] Rosner,[24] Sigwald and Bonduelle,[25] Urechia,[26] and others. Both observations seem to indicate an objective neurological symptomatology in response to perception of color, which usually does not manifest itself by somatic symptoms.

Interestingly, the three noncommitted patients with Parkinsonism showed no test differences (intelligence and Rorschach responses) which would serve to distinguish them from the institutionalized members of this group. It must be admitted, however, that these three subjects were not without psychiatric symptoms. One showed periodic impulsivity of behavior and incoherent speech; another had obvious paranoid traits, while the third had a mild chronic depression. There were also no essential test differences to be found between patients with Parkinsonism of encephalitic origin and patients whose disease was of nonencephalitic (arteriosclerotic and degenerative) origin.

However, in Parkinsonism, the age of onset can be shown to bear a direct relation to the extent of personality deterioration. The subgroup (four cases) with onset in adolescence (age range, 11 to 17 yr.) showed the more pronounced narrowing of personality resources ("constriction" and "coarctation"), the poorer mental control (poorer form level: higher F — %; high W%, largely Wv), and complete absence of color response. The last factor would suggest, as mentioned above, an extension of the lesion to involvement of the diencephalon. Clinical findings were in agreement with this test result. Color response, however, was still present in three of the cases of late onset. Nonetheless, the mean intelligence quotients of these two subgroups are equivalent (Table 2).

Comparison of the patients in the hyperkinetic group with onset in late adulthood or the senium with those whose onset was in adolescence or early adulthood (average ages 63 and 13.5; ranges, 52 to 74 yr. and 1 to 35 yr., respectively) revealed no essential differences.

While intellectual preservation does not seem dependent on the age of onset of either the hyperkinesis or the Parkinsonism, it was found to be significantly different for these groups. Thus, it might be argued that the differences in the Rorschach results presented in Table 1 are largely dependent on this significant difference in intelligence between the groups (respective mean intelligence quotients, 66.0 and 104.3).

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23. Stern, F.: Epidemische Encephalitis (Economoische Krankheit), in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, Vol. 13.

24. Rosner, A.: The Psychiatric Sequelae of Epidemic Encephalitis, in Neal, J. B.: Encephalitis: A Clinical Study, New York, Grune & Stratton, Inc., 1942.

25. Sigwald, J., and Bonduelle, M.: Les accès psychiques paroxystiques de la maladie de Parkinson postencéphalitique, équivalents des accès oculo-céphalogyres, Rev. neurol. **81**:667-672, 1949.

26. Urechia, C.: Les crises diencéphalitiques, Encéphale **38**:21-31, 1949.

However, the generally comparable occurrence of "negative symptoms," that is, the absence of features normally present, in both our hyperkinetic and our akinetic group indicates that the level of intelligence itself does not play the commanding role in personality defects as they are revealed by the Rorschach test. Rather, these personality defects are dependent on the localization of the brain lesion, as shown below. This finding seems in keeping with neuropsychiatric experience. The better intellectual preservation among patients with Parkinsonism may often serve as one of their identifying characteristics.

In view of the low intelligence quotients in the hyperkinetic group (mean intelligence quotient, 66.0), it seemed profitable to compare these results with those of Beck [27] for feebleminded patients. The narrowed personality resources, stereotypy, infrequent good original responses (O +) and low M responses were decidedly common to both. While Beck reports a higher number of responses for his mentally defective subjects, this may be due to his principle of excluding records with less than 10 responses (R ranged from 4 to 19 in our hyperkinetic group, being less than 10 for six patients). The difference in manner of approach

TABLE 2.—*Rorschach Test Results of Parkinsonian Subgroups*

	No.	Average Age of Onset	M	FM	m	k	K	FK	F	Fc	c	C′	FC	CF	C	R	Rejections
Early onset.....	4	13.8	0.75	2.5	...	0.25	...	...	5.75	0.5	...	...	...	...	...	9.7	2.2
Late onset.....	6	46.8	1.0	3.5	...	....	...	...	3.5	0.7	0.2	...	0.5	0.5	...	9.8	2.8

	F%	F-%	Ster. A%	W%	D%	d%	Dd8%	O%	O+%	Piotrowski Av. R. T.	Ross Insta-bility Sign	Ross Disn-bility	Form Level Total	Form Level Av.	Wechsler I. Q.	Wechsler E. Q.
Early onset.....	63.2	32.5	72.2	71	26	..	3	5	1.5	10.6*	2.7	19	14.5	7.4	0.5	100	92
Late onset.....	35.3	7.3	64.0	42	40.5	12	5	5	5.0	22.4	2.0	21	7.5	10.0	1.1	107	92

* One patient with extreme bradyphrenia is not included in this calculation.

(response location) is quite the reverse. Beck reports few whole and many detailed responses as typical of the mentally defective patient. Our findings indicate an overemphasis on whole responses and consequent underemphasis of normal details [28] in cases of localized brain lesions. It would appear that the mentally defective patient was never capable of highly organizing his perceptual field, whereas the demented patient with organic disease, though once capable, now perceives his field only vaguely but preserves the manner of approach of a once higher level of intellectual functioning. This Rorschach finding is thus in agreement with the generally accepted psychiatric view of the differences between mental deficiency and dementia.

Fortunately, we were able to obtain one patient with hyperkinesis who was intellectually well preserved (intelligence quotient, 111) and leading a relatively normal married life (housewife and recent mother, 33 yr. of age). Not only were the pathological responses described under "release phenomena" not present, but signs of psychological deficit, or "negative symptoms," could not be detected.

27. Beck, S.: The Rorschach Test as Applied to a Feebleminded Group, Arch. Psychol. Vol. 21, no. 136, 1932; The Rorschach Test and Personality Diagnosis: I. The Feebleminded, Am. J. Psychiat. **10**:19-52, 1930.

28. Klopfer and Kelley,[9] p. 258.

Her responses displayed excellent formal organization and reflected the presence of creativity (M), sensitivity (Fc, Fk, m), and emotional rapport (FC). There were no rejections and none of Piotrowski's signs, and the Ross "instability-disability" ratio was well within the normal range. Though the quality of response was excellent, the manner of approach, with emphasis on whole responses, was that common to our patients with extrapyramidal lesions,[29] while, as was found typical for patients with hyperkinesis, her Rorschach reaction times were unusually rapid. However, the record might also be considered normal for the still developing, but not yet mature, personality structure, as it showed the "adolescent" features of M < FM and FC < CF, (H), and (A) and the presence of "school-girl" phrases in response. This subject first evidenced her hyperkinesis between 13 and 14 yr. of age, and it would seem, from the Rorschach record, that her personality structure had remained arrested at that stage. Nonetheless, this record has pronounced differences from those of our hyperkinetic group.

It is considered that the hyperkinetic movements are due to a lesion interrupting an inhibitory corticostriate circuit, but a lesion which in itself is not regarded as causing impairment of intelligence. Thus, we must conclude that our patients with hyperkinesis, except for the one aforementioned, had a cortical impairment apart from the lesion causing the hyperkinesis.[30]

Only one systematic Rorschach investigation of the hyperkinetic type of extrapyramidal lesions appears to have previously been reported. Krauss,[31] also cited by Booth,[32] studied 24 cases of chorea minor, and his findings largely agree with the results of the present investigation. He noted a poverty of response, both in coarctation and in productivity, and a response of poor quality, with stereotypy. Several of his results, however, are in striking contrast not only with the present findings, but with the "generalized organic" picture, as commonly reported in the literature. Slightly more than 50% of his patients gave space responses (reversal of figure and ground)—a rare type of response in subjects with organic brain damage. While our material does not include any cases of chorea minor, it would seem, if Krauss's finding can be corroborated, that this type of response may serve as a point of distinction of the personality changes resultant from this illness. This might also apply to the shading responses which he describes as frequent in cases of chorea minor.

We are able to compare our findings in patients with Parkinsonism with those of several investigators. Veit [3b] distinguished two forms among the Rorschach records of 28 patients with postencephalitic Parkinsonism. One displayed marked perseveration, while the other did not. Of our records, two were of the "perseverative" form and displayed the severe coarctation (M : sum C = O : O), exceedingly low form level (form level total, — or O), absence of good original

29. And also, of course, to many normal subjects displaying a superior organizational capacity and/or ambitiousness.

30. The Rorschach records of our cortical and hyperkinetic patients show many test similarities (with the exception of reaction time) which may well be accounted for by this assumption.

31. Krauss, S.: Persönlichkeitsveränderungen nach Chorea minor, Schweiz. Arch. Neurol. u. Psychiat. **34**:94-142, 1934.

32. Booth, G.: Objective Technics in Personality Testing, Arch. Neurol. & Psychiat. **42**:514-530 (Sept.) 1939.

responses, and a high degree of stereotypy, in addition to perseveration, as described by Veit. While some of the records of our nonperseverative subjects contained one or two of these signs, none showed perseveration or an inadequate form level ($F + \% < 70$). It might also be noted that the nonperseverative records more closely resembled the so-called neurotic pattern, the perseverative records being more typically organic and yielding evidence of personality deterioration. Gross intellectual defect does not seem to be a requirement of this perseverative record. While the intelligence quotient of one patient was 66, that of the other was 104, indicating an intelligence within the average range (for the latter).

A narrowed range of the thought content (stereotypy) was present in our records of patients with Parkinsonism, in accordance with the findings of Veit,[3b] Endacott,[3c] and Steck.[3d] This was also a feature of the test results of the hyperkinetic group, though not as pronounced.

While anxiety has been described[3a, c] in the Rorschach records of patients with postencephalitic Parkinsonism, it is not stated whether this assumption is based on the occurrence of certain chiaroscuro responses (shading responses, k, K, FK). In any event, these responses have been conspicuous by their absence in the present material, occurring in but one of our patients with Parkinsonism. They were completely absent in the records of our hyperkinetic group.

While it is believed that the results of the present investigation, as well as our previous findings,[2] offer evidence that the particular localization of the brain lesion has certain specific influences on the response to the Rorschach test, in addition, perhaps, to the production of an "organic" test record, certain limitations must be stated. The degree of application to records of children and adolescents is doubtful, especially where it is considered that the lesion may have been responsible for an aberration in development, rather than for production of a defect in relatively mature personality structures, as is the case when the lesion occurs in adult life. In any event, our material is based on adults, and we should hesitate to transfer the conclusions reached to other age groups.

Though specific test features have been indicated for the various localizations of brain lesions investigated, we would lay especial emphasis on the statement that these features *cannot* be interpreted in reverse. If there exists a diencephalic lesion, color response, it appears, will be absent. But, if color response is absent, a diencephalic lesion is not necessarily indicated.[2] Absence of color response has frequently been reported as common in cases of depression[33] and neurotic inhibition. Further illustration of the caution that must be exercised is given by the examples of stereotypy ($A\% > 50$) and limited productivity (R low, < 15). While stereotypy is common in the Rorschach records of patients with organic disease, it has also been described as characteristic of the neuroses.[34] Limited productivity in the records of mental defectives,[27] and of depressive[33b] and

33. (*a*) Guirdham, A.: The Diagnosis of Depression by the Rorschach Test, Brit. J. M. Psychol. **16**:130-145, 1936. (*b*) Levy, D., and Beck, S.: The Rorschach Test in Manic-Depressive Psychosis, Am. J. Orthopsychiat. **4**:31-42, 1934. (*c*) Young, R.: The Rorschach Diagnosis and Interpretation of Involutional Melancholia, Am. J. Psychiat. **106**:748-749, 1950.

34. Bark, B., and Baron, S.: Neurotic Elements in the Rorschach Records of Psychotics, Ror. Res. Exch. **7**:166-168, 1943. Maile, F., and Harrower Erickson, M.: Personality Structure in the Psychoneuroses, ibid. **4**:71-74, 1940.

schizophrenic [35] patients has been reported as a barrier to adequate appraisal of the personality structure of many such patients. We note that but five patients (25%) in the present groups gave 15 or more responses to the test.[36]

COMMENT

The results of psychological tests tend to confirm the clinical findings. In accordance with other authors,[37] we have found that the intellectual capacities themselves are preserved in the Parkinsonian group, while the bradyphrenia, mood changes, and character disturbances, often observed clinically, are also manifest in our test results.

Our hyperkinetic patients, on the other hand, showed a notable intellectual impairment, both in the Wechsler-Bellevue and the Rorschach tests, thereby corroborating this aspect of the clinical picture. In the present material, the hyperkinesis was associated either with a significant intellectual deficit (frequently, mental deficiency) or with mental deterioration (dementia) of arteriosclerotic or senile origin.

Impairment of intelligence, however, is generally considered as dependent, not on lesions of the extrapyramidal system, but, rather, on those of the cortex.[37a] Hence intellectual impairment (in cases of intracranial damage to the brain) may serve as an indication of extension of the lesion into the cortex. It is suggested that generally our Rorschach findings in the hyperkinetic group are also more connected with significant impairment of the cerebral cortex.[38] The Rorschach findings in the Parkinsonian group, however, may well be related to the lesion of the lower part of the basal ganglia (pallidum-substantia nigra) and/or the hypothalamus.[2]

In agreement with clinical observation that pseudoneurotic symptoms (compulsions, tics, etc.) are often found with postencephalitic Parkinsonism,[39] the majority of our patients displayed "neurotic signs" in their Rorschach records. Therefore, some caution, it would appear, must be exercised in the interpretation of the Rorschach "neurotic" signs. They may not be solely characteristic of the neuroses but may, perhaps, be an expression of an underlying mechanism which can become apparent under different conditions. While one of these conditions may be a psychogenic conflict leading to neurosis, the other may, perhaps, be an

35. Dimmick, G.: An Application of the Rorschach Ink Blot Test to Three Clinical Types of Dementia Praecox, J. Psychol. **1**:61-74, 1935-1936.

36. While less than 15 responses may be insufficient for analysis of the personality structure, we have found such records to be characteristic of patients with certain types of brain lesions. To exclude these records from consideration would prevent a Rorschach evaluation of typical severe organic conditions.

37. (*a*) Cobb, S.: Emotions and Clinical Medicine, New York, W. W. Norton & Company, Inc., 1950, p. 208. (*b*) Steck.[9d] (*c*) Rosner.[24]

38. This tends to be corroborated by a comparison of the Rorschach records of our cortical and hyperkinetic groups.

39. Stern.[23] Rosner.[24] Sigwald and Bonduelle.[25] Urechia.[26] Jahrreiss, W.: Störungen des Denkens, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1928, Vol. 1, p. 581.

organic brain disease affecting certain structures in the brain whose function appears connected with the basic features of personality.

Beck [40] pointed out:

> We cannot at all times interpret the same Rorschach factor as having precisely the same personality value. . . . But a closer scrutiny of all the personality values of any one of the factors shows these differences to be differences only in respect to their social values. There is an identity of psychological process which is finding expression.

In this regard, it is interesting that the Rorschach records of our patients show a high intragroup similarity.[41] Thus, it would seem that the particular lesion exerts an influence on responses to the Rorschach test which is predominant over the original personality structure.

Seen from a broader angle, our results indicate that organic brain lesions of different localization influence the personality structure in different ways. We have found that in patients with diseases which affect only or predominantly the cortex, the Rorschach test will reveal a different type of personality change than in patients with diseases which are localized more to the brain stem. That many organic diseases show common Rorschach features may be due to the diffuse character of these diseases, affecting subcortical as well as cortical regions.

Finally, the Rorschach test results may be utilized in the traditional manner—to determine potential behavioral characteristics, personality resources, and/or the extent of impairment. From these findings, the potential result of therapy can often be inferred.

CONCLUSIONS

1. Rorschach studies of subjects with a localized brain lesion can be undertaken with a view in keeping with neurological principles.

2. Organic brain lesions are seen to exert a specific influence on personality in accordance with their particular localization.

3. Many of the Rorschach features of patients with brain lesions may be likened to "negative symptoms" in the sense of Jackson, in that they are features of loss or psychological deficit; that is, there is absence of many features which would be expected in the normal record. "Release phenomena," or pathological expressions, are also evident in the responses of our subject.

4. Lesions of the basal ganglia do not appear to cause intellectual impairment, but, rather, are responsible for personality changes of mood and/or impulsivity, in addition to the motor phenomena. Intellectual impairment, in subjects with brain lesions, is indicative of involvement of the cerebral cortex.

5. The Rorschach records of patients with brain disease (or brain injury) may usually be distinguished from those of mental defectives, even though their measured intelligence (intelligence quotient) may be equivalent.

6. The so-called neurotic symptoms frequently seen in Parkinsonism appear to have their basis in the particular localization of the brain lesion.

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40. Beck, S.: Psychological Processes in Rorschach Findings, J. Abnorm. & Social. Psychol. **31**:482-488, 1937.

41. Kral and Dörken.[2] Dörken, H., Jr., and Kral, V. A.: The Psychological Differentiation of Organic Brain Lesions and Their Localization by Means of the Rorschach Test, read before the annual meeting of the American Psychiatric Association Convention, Cincinnati, 1951.

7. The age of onset is seen to bear a direct influence on personality changes in Parkinsonism. This could not be demonstrated in our hyperkinetic group.

8. Within the groups studied, age of onset did not, of itself, appear to be related to the extent of intellectual impairment.

9. The results of psychological tests corroborate the clinical findings. They also yield valuable information regarding potential behavior, personality structure, and extent of impairment.

SUMMARY

A "comparative psychological study of the hyperkinetic and akinetic extrapyramidal disorders" is presented. The results of the Rorschach (personality) and Wechsler-Bellevue (intelligence) tests are evaluated, with particular emphasis on the influence of the differing localization of brain lesions. The results are based on investigation of 10 adult subjects in each group, plus two illustrative cases.

SPONTANEOUS SUBARACHNOID HEMORRHAGE OCCURRING IN NONECLAMPTIC PREGNANCY

JOHN W. CONLEY, M.D.
AND
CARL W. RAND, M.D.
LOS ANGELES

WITH THE development of cerebral angiography, as pioneered by Egas Moniz,[1] exact visualization of the source of spontaneous subarachnoid hemorrhage is often possible, and its suitable surgical management may be suggested. This problem becomes more urgent and difficult when such a hemorrhage complicates normal pregnancy. There is little to be gleaned from the experience of others, as relatively few cases of spontaneous subarachnoid hemorrhage occurring in the course of normal gestation have been reported. On the other hand, many instances of such hemorrhages have been encountered in eclamptic women. In this communication we are confining our discussion strictly to the noneclamptic patient. In reviewing the experiences of other authors, we realize that it has been difficult for them to exclude some cases of borderline toxemia when reporting on this complication of pregnancy. Consequently, we feel that the statistics given to date are not altogether correct. While angiography may offer in many cases a means of disclosing the source of the hemorrhage, other clinical and laboratory tests should reveal whether or not a toxemia exists. In rare instances, as reported by Richardson and Hyland [2] and Rhoads,[3] the two conditions may occur simultaneously.

It is not our purpose to discuss in detail the etiology of such a hemorrhage, as many excellent papers have been written dealing both with the clinical syndrome and with the multiple pathological entities responsible for this condition. Garber and Maier [4] suggested numerous cases but were of the opinion that intracranial aneurysm was the most frequent. Clinical and pathological studies of subarachnoid and intracerebral hemorrhages caused by the rupture of berry aneurysms made by

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From the Department of Neurological Surgery, Los Angeles County Hospital and the School of Medicine, University of Southern California.

1. Egas Moniz: Intracranial Aneurysm of the Right Internal Carotid Artery Made Visible by Cerebral Arteriography, Rev. d'oto-neuro-ophth. **11**:746-748 (Dec.) 1933.

2. Richardson, J. C., and Hyland, H. H.: Intracranial Aneurysms: A Clinical and Pathological Study of Subarachnoid and Intracerebral Hemorrhage Caused by Berry Aneurysms, Medicine **20**:1-81 (Feb.) 1941.

3. Rhoads, E. E.: Congenital Aneurysm of the Circle of Willis Associated with Pregnancy, Am. J. Obst. & Gynec. **54**:533-536 (Sept.) 1947.

4. Garber, M., and Maier, R. R.: Pregnancy Complicated by Subarachnoid Hemorrhage, Am. J. Obst. & Gynec. **56**:1174-1177 (Dec.) 1948.

Richardson and Hyland [2] and Martland [5] are outstanding. Dandy's [6] monograph on intracranial arterial aneurysms stands without peer and contains an exhaustive bibliography on the subject.

The clinical picture of spontaneous subarachnoid hemorrhage is strikingly similar in all cases and may occur at any age. The bleeding almost invariably results from leakage of a faulty vessel wall, rupture of an aneurysm, or some other vascular anomaly. Almost without exception, the patient is suddenly seized with severe headache, usually in the occipital region. This may be accompanied with nausea and vomiting. Derangement of the conscious state follows, which varies from confusion to coma, depending on the degree of extravasation. Stiffness of the neck is almost always present. On occasion, bleeding may occur into the brain substance itself, giving rise to localizing signs of hemiplegia, aphasia, hemianopsia, or inequality of the pupils, depending on the location of the clot. Not infrequently the patient will have convulsions. The presence of blood in the spinal fluid is the *sine qua non* upon which the diagnosis rests. This criterion was fulfilled in all our cases by lumbar puncture, except in Case 8, in which blood was found in the fluid at autopsy.

REPORT OF CASES

CASE 1.—*Spontaneous subarachnoid hemorrhage in the sixth month of pregnancy in a woman aged 21, with recovery and instrumental delivery at term, followed by uneventful gestation and normal delivery two years later.*

H. A., a Caucasian woman aged 21, entered the Los Angeles County Hospital as a poliomyelitis suspect on Aug. 22, 1942. She complained of headaches of three days' duration, fever for two days, and nausea and vomiting on the day of admission. She had sudden onset of severe occipital headache, which radiated down the spine to her hips. There was no history of trauma. She stated that she was six-months pregnant at the time of admission.

Examination revealed a blood pressure of 120/70, a pulse rate of 120, a respiration rate of 24, and a temperature of 100.8 F. She was alert and cooperative, but apprehensive. Neurological examination revealed an essentially normal state, except for Kernig's sign. Lumbar puncture revealed a pressure of 125 mm. of water and blood-tinged fluid; the Pandy reaction was 3+; there were 190 white cells (65% polymorphonuclear leucocytes) and 24,000 red blood cells, per cubic millimeter.

The patient responded favorably to repeated spinal punctures and was discharged to the care of her private physician on Sept. 4. He later revealed that on Nov. 28 the patient was delivered by low forceps, under inhalation anesthesia, of a viable male infant, weighing 7 lb. 1 oz. (3,203 gm.). At that time it was noticed that the patient had some weakness of the left rectus muscle. He further stated that he attended her during a subsequent pregnancy and delivered her without incident, in 1944. At present she is said to be in good health and conducting her normal duties as a housewife.

CASE 2.—*Fatal spontaneous subarachnoid hemorrhage occurring four hours post partum in a multipara aged 33.*

S. M., a multipara aged 33, was delivered spontaneously of a living infant on Oct. 31, 1945, by Dr. S. D. Hart, who has permitted us to report this case. She had a convulsion just prior to the onset of labor; her delivery was normal and was carried out under anesthesia produced by intrathecal injection of pipercaine (metycaine®), and her blood pressure at the time registered 130/70. The spinal fluid was not observed to be bloody at the time of delivery. Immediately after delivery she complained of severe headache, had rapid development of decerebrate rigidity

5. Martland, H. S.: Spontaneous Subarachnoid Hemorrhage and Congenital Berry Aneurysms of the Circle of Willis, Am. J. Surg. **43**:10-19 (Jan.) 1939.

6. Dandy, W. E.: Intracranial Arterial Aneurysms, Ithaca, N. Y., Comstock Publishing Co., Inc., 1944.

with a bilateral Babinski sign and went into coma. A lumbar puncture at this time revealed bloody cerebrospinal fluid under a pressure of 60 mm. of water. Urinalysis showed a specific gravity of 1.026, a 1+ reaction for albumin, and no sugar or casts. The carbon-dioxide-combining power of the blood was 32 vol. %; uric acid measured 2.1 mg., and calcium 9.6 mg., per 100 cc. Six hours later the patient died. Autopsy revealed that the medulla, pons, and base of the midbrain were covered with freshly clotted blood, which appeared to be subarachnoid. The hemorrhage extended into the lateral ventricles. The vessels comprising the circle of Willis were normal, and no aneurysm was found elsewhere in the arterial tree. The exact source of hemorrhage was undetermined.

CASE 3.—*Spontaneous subarachnoid hemorrhage occurring at term in a multipara aged 26. Caesarean section, resulting in birth of a living 8½ lb. girl. Recovery of mother.*

On June 5, 1948, the patient, B. V., aged 26, was seen in consultation by one of us (C. W. R.) with her physician, Dr. Jay B. Cosgrove, through whose courtesy this report has been made available. She was at term, and in active labor with her second pregnancy, when she was suddenly stricken with a terrific headache. When seen, she was perfectly clear and conscious. Her headache had been eased with morphine, and the pupils were equal but very small. They reacted poorly to light, and the fundi could not be satisfactorily seen. She used all extremities well, and the deep reflexes were present, active, and equal on the two sides. There were no abnormal reflexes of the Babinski group. Her neck was rigid, and Kernig's sign was present bilaterally. Examination of the spinal fluid revealed gross blood, the red blood cell count being 2,070,000, 2,080,000, and 2,080,000 in the three tubes, respectively. The urine was yellow, clear, and neutral in reaction, and showed a specific gravity of 1.005. There was no albumin, sugar, or acetone, but an occasional finely granular cast was observed. The blood pressure was 126/80.

Immediate Caesarean section was advised and she was delivered of a living 8½-lb. (3,856-gm.) girl. When she was next seen, one week later, her headache had disappeared, but she complained of dizziness. Neurological examination showed an entirely normal status. It was recommended that she stay in bed for five weeks.

Clearly, this woman suffered from a spontaneous subarachnoid hemorrhage when the term of her pregnancy was fufilled. It was felt safer to deliver the baby by Caesarean section than to allow her to undergo the strain of labor, which we believed might aggravate the subarachnoid bleeding. Subsequent events proved that the decision was sound. When she was seen a year later, she was in excellent health and brought up the question of further pregnancies. She was advised not to consider this, as the possibility of another subarachnoid hemorrhage could not be disregarded.

CASE 4.—*Spontaneous subarachnoid hemorrhage appearing immediately post partum. Subsequent transient aphasia and paralysis of right side of face, believed due to hemorrhage from a venous anomaly, as shown by angiography.*

Through the courtesy of Dr. Emil Seletz, we are permitted to report the case of Mrs. G. F., a primipara aged 29, who gave birth to a male infant on Jan. 2, 1949. At that time her blood pressure was 180/110. She was said to have had an unusual amount of headache. Her urine was slightly cloudy, with a specific gravity of 1.012, gave a 1+ reaction for albumin, and contained no sugar or casts. After her delivery, a note was made that she should be watched for possible postpartum toxemia. The headache, which appeared shortly before delivery, continued, and by Jan. 6 nuchal rigidity had developed. At that time her temperature was 101.4 F.; she was alert and showed no localizing neurological signs. Her reflexes were normal in all respects. Examination of the spinal fluid displayed an initial pressure of 235 mm., which was reduced to 100 mm. by the removal of about 10 cc. of grossly bloody fluid.

A second lumbar puncture, on Jan. 7, showed the fluid still to be grossly bloody and under 100 mm. of pressure. Her temperature at that time was 103 F.; the blood pressure, 145/90, and the urine normal. Three days later there developed signs of motor aphasia and definite weakness of the right side of the face. An electroencephalogram at this time showed a definite focus of slow-wave activity in the left temporal lead. On Jan. 18, Dr. Seletz performed an angiographic examination, which revealed a large anomalous vein appearing during the arterial phase (Fig 1). All neurological signs cleared up, and the patient was fully recovered one year later.

CASE 5.—*Spontaneous subarachnoid hemorrhage during labor in a multipara aged 34. Stormy convalescence, associated with mental confusion. Failure of angiography to disclose source of hemorrhage.*

Dr. Frank M. Anderson has made available the following record of a patient who came under his observation. G. V. quadrigravida, tripara, aged 34 entered the hospital in labor, complaining of severe frontal headache and vomiting. Gestation had been normal in all respects. Her blood pressure was 120/70, and the urine was normal except for a 1+ reaction for albumin. After the normal delivery of a living infant she had a generalized seizure, and could not then be aroused. There was stiffness of the neck but no paresis of any of the extremities. The pupils were round, equal, and reactive; the fundi were normal, except for slight blurring of the nasal margin of the right disk. The knee jerks were hyperactive, and the Babinski sign was present bilaterally. Lumbar puncture revealed a grossly bloody fluid, under a pressure of 120 mm. of water.

During the next two weeks the patient passed through a stormy course, with gradual improvement. At first both eyes were deviated externally, and four days later mild nystagmus

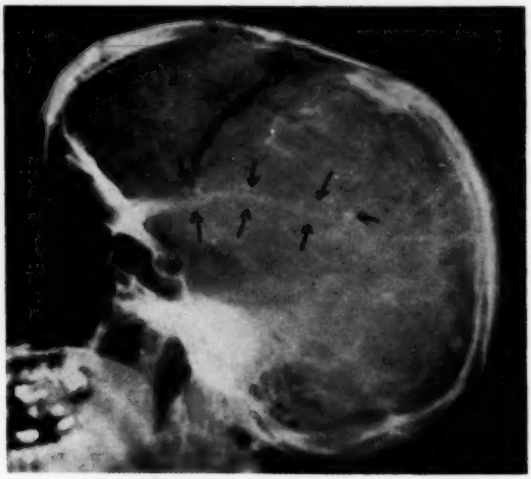

Fig. 1 (Case 4).—Angiogram showing large anomalous vein appearing in the arterial phase. Courtesy of Dr. Emil Seletz.

in all directions appeared. Because of this, it was thought that her hemorrhage arose near the midbrain. She later passed through a period of mental confusion and disorientation. On Nov. 15, 1949, an electroencephalogram showed many large slow waves, of 1 to 2 cps, in both occipital and temporal lobes. On Nov. 16 angiograms of the right carotid and vertebral arteries were made, and, again, on Nov. 29 angiographic study of the left internal carotid artery was performed. No aneurysm was revealed by any of these studies, although a small collection of the contrast medium in the region of the right posterior communicating and basilar arteries suggested an anomaly. Despite angiography, the source of hemorrhage was not determined. At the time of this writing, the patient is fully recovered and engaging in her usual activities.

CASE 6.—*Spontaneous rupture of aneurysm in frontal lobe in sixth month of pregnancy, demonstrated by angiography and treated surgically, with recovery.*

A white married woman aged 26 entered Huntington Memorial Hospital Dec. 31, 1949, under the care of Dr. C. Hunter Sheldon, who furnished an abstract of her history.

On the evening prior to admission she had been found on the bathroom floor, unconscious and with evidence of having vomited. She was six months pregnant at the time. The past history revealed nothing significant except for fainting attacks one year previously.

On examination the patient appeared stuporous, and the right pupil was dilated and did not react to light. She showed repeated convulsive movements of the right upper and lower extremities and was incontinent. The deep reflexes were hyperactive, and a Babinski sign was present bilaterally. Lumbar puncture yielded grossly bloody spinal fluid, with an initial pressure of 220 mm. Subsequent visual-field studies revealed loss of vision in the right eye except in the upper nasal quadrant. An angiogram of the right cerebral artery, performed on Jan. 17, 1950, revealed evidence of a ruptured aneurysm arising from a branch of the anterior cerebral artery on the right side (Fig. 2).

A right transfrontal craniotomy was performed by Dr. Sheldon on Jan. 23. The chiasm and the right internal carotid artery were explored and appeared to be normal. The anterior cerebral artery was explored as far as it could be traced from below, and then the right frontal lobe was reflected from the midline and the remaining portion of the anterior cerebral artery was visualized. No aneurysmal sac was seen. When the frontal lobe was elevated, one area appeared slightly yellowish, and on the mesial aspect a portion of it was removed by suction.

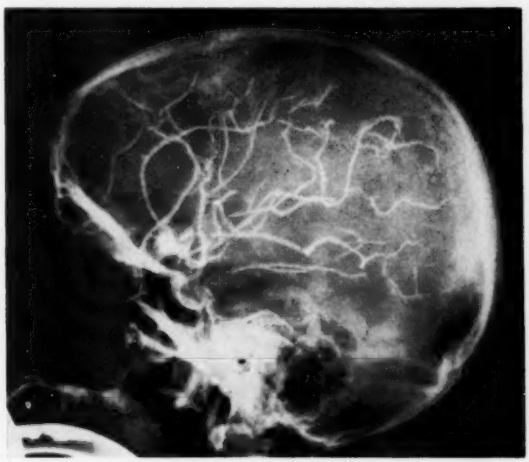

Fig. 2 (Case 6).—Cerebral angiogram showing ruptured aneurysm of right anterior cerebral artery. Courtesy of Dr. C. Hunter Sheldon.

There appeared to be yellowish discoloration near one of the anterior branches of the anterior cerebral artery, apparently at the point at which the aneurysm ruptured. This vessel was clipped and the dissection carried laterally into the middle of the frontal lobe, where a black clot, about 4 cm. in diameter, was seen, surrounded by a zone of yellowish traumatized brain tissue. The entire hematoma was removed, and in the base of the cavity one large vessel was visualized and clipped. Two Penrose drains were left as a precaution, and the wound was closed in layers.

The postoperative course was slow, but one of progressive improvement. For a time the patient had frequent visual hallucinations, but these became infrequent. Vision in the right eye showed little improvement. She was discharged on Feb. 17. On April 6 she was readmitted and underwent a Caesarean section, in the 39th week of her pregnancy. The immediate convalescence was uneventful, and she was discharged on April 14. Later, however, a psychosis developed, which cleared up under appropriate treatment.

CASE 7.—*Spontaneous subarachnoid hemorrhage in the sixth month of pregnancy in a primipara, aged 32. Uneventful delivery by Caesarean section at term. Uncomplicated convalescence.*

Mrs. B. M., aged 32, was seen in consultation with Dr. Morris Steinman at St. John's Hospital on June 17, 1950, because of recent severe headaches. At that time she was seven months along in her first pregnancy. Eight years, and again five years, previously she had gone through

periods of severe headaches, which lasted a few days and then disappeared. On June 10, 1950, she had sudden onset of headache and "spots before her eyes." The headache continued intermittently for the next three days and on June 13 became excruciating. The greatest pain was in the occipital region, later radiating through the temples. On June 15 examination of the spinal fluid revealed xanthochromic fluid under pressure of 290 mm. of water. It contained 2,834 red blood cells per cubic millimeter. The urine was normal except for a slight trace of albumin. The blood pressure was 110/80. At the time of examination the headache had eased to a considerable extent. Her neck was not stiff, and Kernig's sign was not elicited on either side. The pupils were equal and reacted well to light and in distance accommodation. The eyegrounds were normal. A complete physical and neurological examination was noncontributory.

It was believed that she had suffered a spontaneous subarachnoid hemorrhage, which began on June 10 and reached its climax on June 13. Presumably, she had had similar subarachnoid hemorrhages eight and five years previously. It was recommended that she remain in bed for

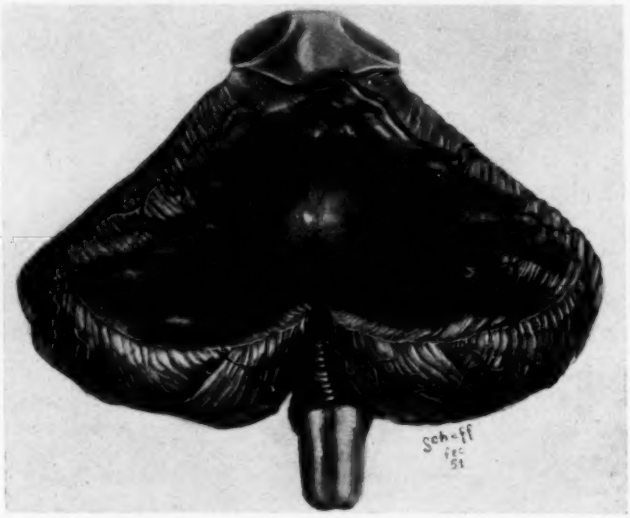

Fig. 3 (Case 8).—Cerebellar angioma. Fatal bleeding resulted in this vascular malformation. Courtesy of Ramón y Cajal Laboratory.

the next six weeks, and it was further advised that delivery be by Caesarean section when she reached term. On July 28 she was delivered of a baby girl by Dr. Louis A. Seigel, who performed a low cervical Caesarean section, with epidural anesthesia. Convalescence was smooth, and she was discharged on the eighth postoperative day in good condition.

She was reexamined on Dec. 8, when she was free of headache and had no other complaints. The neurological status was entirely normal, and her blood pressure measured 120/70 in the right arm and 125/75 in the left arm. She has never shown sufficient signs to indicate the source of her hemorrhage or its location, although a berry aneurysm is suspected. At this writing, the question of suggesting angiography is under consideration.

CASE 8.—*Fatal hemorrhage from a cerebellar angioma in a woman five-and-one-half-months pregnant.*

Permission to report this case was granted by Dr. Cyril B. Courville, director of the Ramón y Cajal Laboratory of Neuropathology. N. D., a white woman aged 30, a multipara five-and-one-half-months pregnant, had been in good health throughout her pregnancy. The systolic blood

pressure, when she was last seen by her private physician, registered from 100 to 110 mm. About 4 p. m. on Aug. 25, 1950, she became dizzy, felt ill, complained of severe headache, lay down on the couch, and died.

Autopsy was performed by the coroner's surgeon, who sent the brain to the Cajal laboratory for study on Aug. 28. The cerebral hemispheres showed a moderate amount of subarachnoid hemorrhage lying within the sulci, chiefly of the ventral and parieto-occipital regions. A small amount of hemorrhage lay at the base, in the cisternal spaces, particularly the cisterna pontis and the cisterna lateralis, which were filled with blood clot. The convolutions appeared slightly flattened. Subarachnoid hemorrhage was also present about the superior portion of the vermis and the posterior margins of both cerebellar hemispheres, apparently compressing the posterior portion of the superior vermis, particularly on the left side. Here a tumor was found, which was firm and had evidently compressed the adjacent superior cerebellar surface. The exact localization of this mass was somewhat difficult to ascertain, but from as careful a reconstruction as

Fig. 4 (Case 8).—Photomicrograph showing vascular structure of cerebellar angioma.

could be made, on the basis of relationships of covering arachnoidal hemorrhage and of confirmation to cut surfaces, it was almost certain that the tumor had the location described and drawn in Figure 3. It was evidently a vascular malformation, for a freshly cut surface showed it to be made up of various-sized vascular channels, between which a condensed connective-tissue stroma was observed. It obviously was the source of the bleeding which cost the patient her life.

Sections made through the cerebellum showed the cerebellar tissue to be extremely atrophic and softened in the region of the malformation. On cutting open the fourth ventricle, one found a cast of this cavity, indicating that hemorrhage took place internally, as well as externally. This was also shown by the presence of clots in the third ventricle, and even to some extent in the lateral ventricles, evidently from retrograde extension. Repeated cross sections of the brain showed this to be true but disclosed no other lesions.

Histopathologic Study.—A block was taken from the dark-colored and spongy-appearing mass in the posterior aspect of the cerebellum, and from this block sections were obtained for study. It was evident that a portion of the mass noted above was made up of congeries of vessels of abnormal size, being excessively large as compared with normal vessels in this region. These

vessels were both arteries and veins and surmounted the regional portion of the cerebellum, which had undergone a degree of atrophy in consequence of the pressure by these vessels (Fig. 4.). Between the abnormal blood vessels was found a heavy connective-tissue stroma, in which collections of lymphocytes existed.

The histologic diagnosis was arteriovenous angiomatous malformation, evidently the source of the fatal subarachnoid hemorrhage.

It is clear that the fatal subarachnoid hemorrhage resulted from a rupture of a blood vessel in a vascular anomaly occupying the superior portion of the vermis and the medial aspect of the superior portion of the left cerebellar hemisphere. The influence of pregnancy is uncertain, for, so far as we know, the patient was under no undue stress at the moment.

TABLE 1.—*Summary of Authors' Cases*

Case	Age	Parity	Blood Pressure	Time of Hemorrhage	Source of Hemorrhage	Character of C. S. F.	Condition of Child	Mode of Delivery	Condition of Mother
A. H. 8/22/42	21	Primipara	120/70	6 mo. pregnant	Undetermined	Blood-tinged	Living, normal	Low forceps	Recovered
S. M. 10/31/45	33	Multipara	130/70	Immediately post partum	Undetermined	Grossly bloody	Living, normal	Spontaneous	Died. Autopsy: basilar hemorrhage
B. V. 6/5/48	26	Multipara	126/80	Term in labor	Undetermined	Grossly bloody	Living, normal	Caesarean section	Recovered
G. F. 1/2/49	29	Primipara	180/110 145/90	Immediately post partum	Angiography; venous anomaly	Grossly bloody	Living, normal	Spontaneous	Transient rt. hemiparesis and aphasia with ultimate recovery
G. V. 10/49	34	Multipara	120/70	During labor	Undetermined by anglography	Grossly bloody	Living, normal	Spontaneous	Transient psychosis, which cleared
H. M. 12/31/49	21	Primipara	Normal	6 mo. pregnant	Ruptured aneurysm of rt. ant. cerebral art.	Grossly bloody	Living, normal	Caesarean section	Transient psychosis, which cleared
B. M. 6/17/50	32	Primipara	110/80	7 mo. pregnant	Undetermined	Xanthochromic	Living, normal	Caesarean section	Recovered
N. D. 8/25/50	30	Multipara	110/?	5½ mo. pregnant	Rupture cerebellar angioma	Not determined	Undelivered fetus	Undelivered	Sudden death; autopsy

The following case is not included as a proved instance of spontaneous subarachnoid hemorrhage during pregnancy, although the clinical picture would strongly suggest it; furthermore, it furnishes evidence that a woman may pass through a normal pregnancy successfully after a known hemorrhage.

F. J., a multiparous, nonpregnant Caucasian woman aged 21, entered the Los Angeles County Hospital on July 25, 1942, having collapsed in coma five days previously. In spite of improvement in her general condition, her headache was so severe that she applied to the hospital for its relief. Her general physical examination was noncontributory. Neurological study showed absence of abdominal reflexes, absence of deep reflexes on the left, and a Babinski sign bilaterally. Her neck was not stiff, but she was still lethargic. The blood pressure was 120/76. Lumbar puncture revealed grossly bloody cerebrospinal fluid, under a pressure of 210 mm. of water. On July 27, a second examination of the spinal fluid still revealed bloody fluid, which was under a pressure of 350 mm. of water. On July 30, a third puncture disclosed xanthochromic fluid, under pressure of 400 mm. of water. After this she generally improved and was discharged on Aug. 14.

The patient reentered the hospital on Nov. 7, 1942, when two-months pregnant, again complaining of severe headaches, with nausea and vomiting of three days' duration. General and neurological examinations revealed nothing abnormal. Her blood pressure was 136/68.

Although the clinical signs strongly suggested a spontaneous subarachnoid hemorrhage, she refused to have lumbar puncture, gradually improved, and was dismissed. This pregnancy, as well as two later ones, according to her story, were terminated by abortion. On Dec. 7, 1944, she was again admitted to the hospital and was delivered at term of a living baby.

At the time of this writing, six years later, she is reported as living and well. Whether she has carried a berry aneurysm or some other vascular anomaly in her brain during all this time is a matter for consideration. She certainly had a spontaneous subarachnoid hemorrhage two months before her third pregnancy, and although its presence was not proved, because of her refusal to have a spinal puncture, the clinical signs pointed to recurrent bleeding during the second month of this pregnancy. The case is of special interest in that the patient was able to endure the rigors of two pregnancies without incident, later had a spontaneous hemorrhage, with recovery, and then passed through a third pregnancy. This accomplishment, in the presence of a supposedly weakened vessel, emphasizes the difficulty of prognosis which confronts the obstetrician when pressed for a decision regarding future pregnancies.

EXPERIENCE OF OTHER AUTHORS

Lazard,[7] in 1899, recorded one of the earliest cases of cerebral hemorrhage in pregnancy appearing in the American literature. His patient, a Caucasian woman, trigravida, secundipara, aged 31, entered the hospital at the onset of labor. She complained at the time of headaches but was delivered spontaneously. The urine showed a slight amount of albumin and a few hyaline casts. During delivery she became lethargic, had convulsions, went into coma, and died four days later. Unfortunately, no blood-pressure reading or examination of the spinal fluid was made, and we cannot be sure that she had a spontaneous subarachnoid hemorrhage. Autopsy revealed hemorrhage from a ruptured artery in the region of the corpus striatum.

That a woman having an aneurysm at the junction of the right internal carotid and the posterior communicating artery may weather several pregnancies without hemorrhage was demonstrated by Symonds [8] in 1923. In his case the fatal hemorrhage occurred in a woman aged 52 who had given birth to three living children and whose fourth pregnancy had terminated in a miscarriage 18 years previously. Her first signs of a threatened aneurysmal rupture, shown by severe headache, pain in the back of the neck, and vomiting, occurred 19 months before death. During convalescence she was said to have been giddy and of unsteady gait, symptoms giving rise to the speculation that she may have had a small leak from the aneurysm at that time. Her final hemorrhage occurred approximately two weeks before her death. It was accompanied with signs and symptoms pointing to a lesion on the right side, as shown by left hemiparesis and Jacksonian twitching of her left leg. A right subtemporal decompression by Dr. Cushing disclosed a tense dura and recently clotted blood, extending in the subdural space over the whole right cerebral hemisphere. Death occurred within a few hours, and autopsy disclosed a small saccular aneurysm, about 8 mm. in circumference, at the junction of the right internal carotid and the posterior communicating artery; a perforation the size of a pinhead was found in the outer wall of this sac. This case is offered as an example of a mother who weathered four pregnancies before finally succumbing to a rupture of an aneurysm 18 yr. later.

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7. Lazard, E. M.: A Case of Cerebral Hemorrhage Following Labor, Philadelphia M. J. **4**:1091-1092 (Dec. 2) 1899.

8. Symonds, C. P.: Contributions to the Clinical Study of Intracranial Aneurysms, Guy's Hosp. Rep. **73**:139-158, 1923.

A careful review of the histories of other mothers who died of ruptured aneurysm would doubtless bring to light many instances similar to the one just described. Sands,[9] in 1929, had an almost identical case, that of a woman aged 47 who had previously given birth to four children. No details regarding these pregnancies were furnished. Autopsy revealed an aneurysm of the right posterior communicating artery. Ohler and Hurwitz,[10] in 1932, reported a case of spontaneous subarachnoid hemorrhage occurring 17 days post partum in a woman aged 27. She died four days after the sudden onset of her symptoms. The blood pressure was 140/90, and the spinal fluid was grossly bloody. Permission for autopsy was not obtained.

King,[11] in 1933, described the case of a multipara aged 19, whose sudden death was caused by massive hemorrhage from the lenticulostriate artery. The woman, at term when the hemorrhage occurred, was delivered by Caesarean section. King emphasized that, as judged by the postpartum finding, the patient had eclampsia, although at no time did she have convulsions. A spinal-fluid examination before death revealed a "bloody fluid at a heightened tension." Had this woman survived, one would almost have been forced to conclude that she had suffered a spontaneous subarachnoid hemorrhage, possibly not on a toxemic basis. Russel,[12] in 1933, reported 26 cases of spontaneous subarachnoid hemorrhage, five of which were of pregnant women. Four of these patients, who do not concern us, had toxemia of pregnancy. The fifth, aged 34, who had no toxemia, had a hemorrhage eight hours after delivery of a normal baby. The author does not give the details of this case, except to state that the patient died and performance of autopsy was not permitted.

Too seldom have cerebral aneurysms in pregnant women been demonstrated by angiography. In 1935 Olivecrona and Riives[13] demonstrated a small arteriovenous aneurysm in the distribution of the left middle cerebral artery by this method (Fig. 5). Their patient, a woman aged 29, in her seventh month of pregnancy, was admitted in a somnolent condition. She had complete right hemiplegia, incipient choking of the right disk, and aphasia. At operation, they removed a large clot, together with a small aneurysm, which had been largely destroyed by hemorrhage. Nine years later she was reported as well, except for slight weakness of the right hand. Unfortunately, no account is given regarding the progress and termination of her pregnancy.

Masten,[14] in 1935, reported 12 cases of spontaneous subarachnoid hemorrhage, in two of which the women were pregnant. In one the hemorrhage was undoubtedly on a toxemic basis; in the other the origin was doubtfully toxemic. In the latter,

9. Sands, I. J.: Aneurysms of the Cerebral Vessels, Arch. Neurol. & Psychiat. **21**:37-46 (Jan.) 1929.

10. Ohler, W. R., and Hurwitz, D.: Spontaneous Subarachnoid Hemorrhage, J. A. M. A. **98**:1856-1861 (May 28) 1932.

11. King, A. G.: Eclampsia Without Convulsions Terminating in Cerebral Apoplexy, J. A. M. A. **100**:15-16 (Jan. 7) 1933.

12. Russel, C. K.: Spontaneous Subarachnoid Hemorrhage, Canad. M. A. J. **28**:133-140 (Feb.) 1933.

13. Olivecrona, H., and Riives, J.: Arteriovenous Aneurysms of the Brain, Arch. Neurol. & Psychiat. **59**:567-602 (May) 1948.

14. Masten, M. G.: Spontaneous Subarachnoid Hemorrhage: Report of 12 Cases, Wisconsin M. J. **34**:168-175 (March) 1935.

hemorrhage occurred in the eighth month of pregnancy. The author did not give further details of the case, but in her table she stated that no aneurysm was found post mortem. In reviewing 105 cases of spontaneous subarachnoid hemorrhage, Strauss and Tarachow [15] (1937) cited two instances in which the hemorrhages occurred in pregnancy. One of the hemorrhages was definitely associated with toxemia and terminated fatally. In their second case, that of a woman aged 24, the first hemorrhage had occurred at the age of 12 yr., with recurrences every two to three years. Her last reported hemorrhage occurred three weeks before delivery, at which time her clinical status was normal. The blood pressure was 120/70, and the spinal fluid was uniformly bloody. She is said to have had another attack six months after delivery but three years later was reported as well. No mention was made as to the mode of delivery, nor was angiography performed.

Fig. 5.—Angiogram showing arteriovenous aneurysm of left middle cerebral artery. After Olivecrona and Riives.[13]

Moskowitz and Schneider,[16] in 1938, described three cases of maternal intracranial hemorrhage complicating labor, in which the bleeding was not associated with toxemia. Their first patient, a primigravida aged 25, had been subject to frequent attacks of syncope during her pregnancy. At no time had she shown signs of toxemia, and her blood pressure, which had previously averaged 110/60, reached 140/100 when she went into labor at term. At the onset of labor she was seized with severe headache and dizziness and within half an hour suddenly became unconscious and died undelivered, 12 hr. 15 min. after the beginning of labor. A catheterized specimen of urine showed a specific gravity of 1.018, a trace

15. Strauss, I., and Tarachow, S.: Prognostic Factors in Spontaneous Subarachnoid Hemorrhage, Arch. Neurol. & Psychiat. **38**:239-258 (Aug.) 1937.

16. Moskowitz, H. L., and Schneider, H.: Maternal Intracranial Hemorrhage Complicating Labor, Am. J. Obst. & Gynec. **36**:489-497 (Sept.) 1938.

of albumin, and an occasional hyaline and granular cast. No sugar or acetone was present. The spinal fluid was not examined. Autopsy revealed extensive hemorrhage occupying all ventricles of the brain and an extensive, irregular hemorrhage in the pons. The authors were of the opinion that an aneurysm in this structure might have ruptured, although it had been destroyed beyond recognition, and therefore escaped notice.

Their second case was that of a woman aged 26, trigravida, secundipara, delivered spontaneously at term, after an uncomplicated prepartum course. Her blood pressure at term was 130/90. Two hours after delivery of an 8 lb. 2 oz. (7,685 gm.) living infant, she suddenly vomited and complained of severe headache, dizziness, pain in both eyes, and dimness of vision. A catheterized specimen of urine showed a specific gravity of 1.010, a trace of albumin, and no sugar or acetone. The nonprotein nitrogen of the blood was normal. The following day lumbar puncture yielded a uniformly bloody spinal fluid. She gradually recovered during the next 67 days, although she continued to complain of headache and dizziness for two years after delivery. The authors believed that the use of 0.5 cc. of posterior pituitary U. S. P. following the delivery of the baby and 1 cc. of ergonovine maleate U. S. P. subsequent to delivery of the placenta may have been the precipitating cause of leakage from an aneurysm, or from a damaged vessel wall, under the strain of hypertension.

Their third case, that of a primipara aged 25, was first seen in the second month of gestation. All went well, with an average blood pressure of 110/80, until she was delivered spontaneously at term of a viable infant, 7 lb. 2 oz. (3,232 gm.) in weight. Ten minutes after delivery of the placenta she suddenly became cyanotic and deeply comatose and died. A postmortem lumbar puncture revealed a uniformly bloody cerebrospinal fluid in all three tubes. Permission for autopsy was not obtained.

The authors conclude: "It is in cases of this sort that one expects to find rupture of a congenital aneurysm if autopsy is performed." Commenting upon the infrequency of subarachnoid hemorrhage complicating labor, they stated as their belief that such accidents occur more frequently than is generally appreciated or reported. They further expressed the belief that the simultaneous administration of two oxytocic drugs following the third stage of labor should be avoided. In addition, they advised that the eyegrounds should be frequently examined whenever a gravid woman complains of headache, and they expressed the belief that when the diagnosis of aneurysm had been made, labor should be terminated by Caesarean section.

Flexner and Schneider,[17] in 1938, reported a case of subarachnoid hemorrhage following the injection of epinephrine, given to control an attack of urticaria in a primipara aged 20 who had been delivered by low forceps two weeks previously. The patient recovered. The authors believed that the epinephrine was the precipitating cause of the bleeding and commented as follows:

> Assuming that there actually existed a congenital aneurysm, how did it withstand the stress and strain of labor only two weeks previously? It is true that the second stage was considerably shortened by low forceps delivery, yet at some time during labor there must have been some

17. Flexner, M., and Schneider, B.: Subarachnoid Hemorrhage Following Injection of Epinephrine, Ann. Int. Med. **12**:876-882 (Dec.) 1938.

strain. It is possible that this exertion weakened the aneurysmal wall sufficiently so that the rise in blood pressure and the increase in cerebral circulation, volume and velocity, after the injection of epinephrine, were able to cause its rupture.

Paucot and Gellé,[18] in 1938, described the case of a woman aged 43 who had a meningeal hemorrhage in the course of her 14th pregnancy. She had been treated for syphilis nine years previously. She was suddenly taken with intense headache, accompanied by vomiting. Clonic convulsions followed. The blood pressure was normal. Spinal puncture revealed uniformly bloody cerebrospinal fluid. The patient went into shock and died. A dead infant was delivered post mortem by Caesarean section. Autopsy disclosed hemorrhage into the left lateral ventricle and an extensive ecchymosis of the entire left cerebral hemisphere. The authors felt there was little doubt that the pre-existing syphilis was a causative factor in precipitating the fatal hemorrhage.

Richardson and Hyland,[2] in 1941, in reviewing 126 cases of intracranial aneurysm, cited only three cases occurring in pregnancy. Only one of these was discussed in detail. In this case a woman aged 38, octigravida, quintipara, was in the fourth month of pregnancy at the time of her illness. She entered the hospital on July 18, 1938, because of a convulsion and was found to have mild toxemia with a blood pressure of 195/120 and slight albuminuria. Spinal puncture revealed grossly bloody fluid. She improved until Aug. 2, when she suddenly became unconscious, but gradually improved after two days. This episode was also accompanied by a bloody fluid. After this, she was found to have left homonymous hemianopsia and hemiplegia and paralysis of the right third cranial nerve. She continued to improve until Aug. 28, when she suddenly died. At autopsy a 1.3-cm. aneurysm was found at the junction of the right internal carotid and the posterior communicating artery. This case is of special interest in that pre-eclampsia tended to mask the real pathologic condition.

In reviewing 150 cases of spontaneous subarachnoid hemorrhage, Magee [19] (1943) stressed that in 90% of the cases the bleeding occurred when the patient was under no physical strain. In 28% the patient was overtaken while in bed or sitting in a chair. He therefore stated: "I suggest that the claim to the precipitating influence of stress and strain is weakened by these findings." A ruptured aneurysm was found in 43 of 58 cases in which autopsy was performed, while in the rest the hemorrhage was confined to the subarachnoid space but no aneurysm could be found. The fact that in such a large percentage of cases hemorrhage occurred while the patient was "at rest" does not necessarily argue that the strain of labor in a pregnant woman might not increase the danger of bleeding.

In 1946, while discussing the problem of cerebrovascular complications of pregnancy, Eller [20] pointed out that all patients with fatal hemorrhages or softening of the brain, even in the presence of hypertension, albuminuria, and convulsions, are not necessarily eclamptic. In 1947 Rhoads [8] reported two cases of congenital aneurysm of the circle of Willis associated with pregnancy. In his first case, in sharp contrast with that of Symonds [8] (1923), the patient had repeated hemor-

18. Paucot and Gellé: Un cas d'hémorragie méningée au cours de la grossesse, Bull. Soc. gynéc. et d'obst. **27**:366-367 (Feb. 23) 1938.

19. Magee, C. G.: Spontaneous Subarachnoid Hemorrhage, Lancet **2**:497-500 (Oct. 23) 1943.

20. Eller, W. C.: Cerebrovascular Complications of Pregnancy, Am. J. Obst. & Gynec. **52**:488-491 (Sept.) 1946.

rhages and died without entering into labor. Her first hemorrhage, associated with grossly bloody cerebrospinal fluid, from which she recovered, occurred in June, 1932. In March, 1943, she again showed symptoms of intracranial bleeding, and lumbar puncture again revealed grossly bloody fluid. In November, 1944, her third hemorrhage occurred, being in all respects similar to those preceding it. Her fourth hemorrhage appeared in February, 1948, when she was in the third month of pregnancy, and she was admitted for consideration of therapeutic abortion. After consultation with several physicians, it was decided to allow her to continue with her pregnancy, but it was stipulated that she should be sterilized 48 hours after delivery. At this time her physicians could not anticipate that a fifth hemorrhage would occur two months later. On April 4, she again was admitted to the obstetrical service, this time in a semicomatose condition. A generalized convulsion followed shortly afterward. Her blood pressure rose to 210/180; the left pupil became dilated, and papilledema with large hemorrhages in both eyegrounds occurred. Her neck was stiff, and a Kernig sign was present. The spinal fluid was bloody, showing an initial pressure of over 350 mm. of water. The blood urea nitrogen was 33 mg.; the serum protein, 7.7 gm.; the albumin, 3.8 gm., and globulin, 4.8 gm., per 100 cc. She died five days later, without regaining consciousness, and autopsy revealed "congenital berry aneurysms of the circle of Willis." It is unfortunate that a more accurate description of the number, size, and exact location of the aneurysms was not given. However, we are led to believe that they were multiple.

Rhoads's second case concerned a woman aged 27 who was delivered on April 12, 1944, and discharged on April 20, in good general condition. On the following day she had several generalized convulsions and was readmitted to the hospital on April 25. She again had convulsions, starting in the right hand and spreading to the right arm and face, when they became generalized. Papilledema also developed. The blood pressure registered 130/80. She exhibited horizontal nystagmus, stiffness of the neck, and hyperactive reflexes. The cerebrospinal fluid was grossly bloody, with an initial pressure of 320 mm. and a final pressure of 150 mm. of water. By May 5 her spinal fluid had become xanthochromic, although the initial pressure was still 350 mm. of water. She is said to have had "mild convulsions for two or three days, with occasional nystagmus," but these disappeared and she was discharged on May 17, with the diagnosis of meningeal hemorrhage, probably from rupture of a congenital aneurysm of the circle of Willis. By way of summary, the author emphasized the seriousness of such vascular lesions; he stated that future pregnancies must be prevented, preferably by sterilization, in patients giving a previous history of subarachnoid hemorrhage. He felt that pregnancy added to the gravity of prognosis and went on to say that "termination of pregnancy is justified in all cases of proved bleeding from intracranial aneurysms."

In discussing spontaneous subarachnoid hemorrhage of aneurysmal origin, Hamby [21] (1948) reviewed 138 cases, 75 of which were of women. No case reports are given, but in a table he stated that four cases occurred during pregnancy or post partum. Two patients recovered, and two died. Garber and Maier,[4] in 1948, reviewed the literature and reported three cases of subarachnoid hemorrhage in pregnant women who did not show signs of toxemia. These authors distinguished

21. Hamby, W. B.: Spontaneous Subarachnoid Hemorrhage of Aneurysmal Origin, J. A. M. A. **136**:522-528 (Feb. 21) 1948.

two types of subarachnoid hemorrhage, which they termed primary and secondary. They believed that in the primary type bleeding occurred into the subarachnoid space from a ruptured adjacent artery and stated that this type was characterized by headache, delayed loss of consciousness, and late signs of paralysis. Such hemorrhages were more frequent in younger persons and were thought to be due to rupture of a small "berry" type of congenital aneurysm. Bleeding in their second type was considered to result from extension of intracerebral hemorrhage into the subarachnoid space and was characterized by early paralysis and rapid loss of consciousness. They expressed the belief that this was oftener the type found in older patients, being based on an arteriosclerotic background.

Their first patient, a Negro woman aged 26, secundigravida, nullipara, was admitted in her eighth month of gestation because of painless vaginal bleeding, nausea, vomiting, and severe frontal and occipital headache. The blood pressure was said to be normal. A catheterized specimen of urine gave a 2 + reaction for albumin and contained hyaline casts. A tentative diagnosis of toxemia of pregnancy and partial placenta praevia was made. When lumbar puncture was carried out for purposes of spinal anesthesia, a uniformly bloody spinal fluid was found. "But its significance was overlooked." The patient was delivered of a living male infant by Caesarean section, but her headache, which theoretically should have diminished after delivery if it had been due to a true toxemia of pregnancy, increased in intensity. This headache was accompanied by stiffness of the neck, and a second lumbar puncture, 10 days later, revealed a grossly bloody fluid, under a pressure of 190 mm. of water. Subsequent spinal-fluid examination showed a clearing fluid, and the patient recovered and was ultimately discharged. Undoubtedly, her cerebral accident, as shown by the presence of bloody spinal fluid, occurred before her Caesarean section but did not receive the proper interpretation. We believe that this patient suffered a second spontaneous subarachnoid hemorrhage about a week post partum.

Their second patient, a white woman aged 26, was hospitalized because of severe headache in the 34th week of gestation. She was nauseated and had vomited. Papilledema was present in the right fundus. She showed moderate nuchal rigidity, and her blood pressure was 110/70. Spinal puncture revealed a uniformly bloody fluid with an initial pressure of 280 mm. of water, which was reduced to 180 mm. by slow withdrawal of fluid. With bed rest she improved, until 22 days later, when she rapidly became comatose and incontinent. A second specimen of spinal fluid, under a pressure of 560 mm. of water, was grossly bloody. The pressure was reduced to 260 mm. by withdrawal of fluid. The following day she was delivered, under spinal anesthesia, by Caesarean section of a viable female infant, weighing 7 lb. (3,175 gm.). The spinal fluid, under an initial pressure of 450 mm. of water, was bloody. The patient regained consciousness after delivery and, after a period of mental confusion, recovered fully. The authors stated that the results of blood chemical and serologic studies were all normal. The extreme gravity of her condition forced the issue of immediate delivery.

Their third patient, a white primipara aged 24, entered the hospital in active labor at term and was delivered of a male infant by low forceps. Because of postpartum bleeding, she received an ampule (1 cc. [10 U. S. P. units]) of "infundin" (posterior pituitary injection U. S. P.) intramuscularly, an ampule (0.2 mg.) of

ergonovine maleate (ergotrate®), and 1 cc. of oxytocin injection U. S. P. (pitocin®) intravenously within 20 min. The following day she was drowsy and on the second day complained of headache. Because of increasing headache and stiffness of the neck, a spinal puncture was done and a uniformly bloody fluid obtained, with an initial pressure of 360 mm. of water, which on withdrawal of fluid dropped to 210 mm. Her blood pressure was 110/70. The following day her spinal fluid was again bloody, and under an initial pressure of 332 mm. of water, which was reduced to 162 mm. by withdrawal of fluid. From this time on her recovery was rapid. It was the authors' belief that this case exemplified the dangers in the liberal use of oxytocics, and they argued that such drugs may increase the blood pressure enough to precipitate the rupture of a congenital aneurysm.

De Carle,[22] in 1949, in reviewing 15,417 deliveries, encountered only three instances of cerebrovascular lesions associated with an otherwise normal pregnancy. His first patient, aged 29, secundigravida, was admitted to the hospital at term in a comatose condition. She had been awakened one hour previously with severe headache and shortly afterward became unconscious and had tonic convulsions, which were severer on the right side. She had been seen four days previously because of severe headache, when her blood pressure was 120/90 and her urine normal. Spinal puncture on admission showed a bloody cerebrospinal fluid, under a pressure of 240 mm. of water; the blood pressure was 110/70, and the urine gave a 3 + reaction for albumin. She was immediately delivered of a normal female infant by Caesarean section but died 24 hours later. During the third trimester of pregnancy three years previously she had had a severe attack of tinnitus and headache. At that time a definite bruit was heard over the left temporal region. Autopsy showed extensive subarachnoid hemorrhage, with a ruptured aneurysm arising from the left communicating artery at its junction with the left internal carotid artery.

His second patient, a primipara aged 23, was seen in the eighth month of gestation complaining of severe headache, vomiting, and urinary incontinence. Her blood pressure was 140/80, and spinal puncture revealed grossly bloody fluid under a pressure of 325 mm. of water. A diagnosis of massive subarachnoid hemorrhage was made, and she was treated by means of bed rest and repeated spinal punctures for the next 18 days. On the 19th day she had convulsions and became comatose and a lumbar puncture showed grossly bloody fluid, under a pressure of 300 mm. of water. A 6 lb. (2,721 gm.) premature infant was delivered by low Caesarean section, but the patient's condition became worse, and, after several convulsive seizures, she died on the following day. Autopsy revealed a small ruptured aneurysm in the anterior communicating artery, the whole subarachnoid and ventricular system being filled with blood.

His third patient is most interesting because of her past history. At the age of 10 yr. she had been hospitalized because of a flaccid paresis of the right side and speech difficulty, a condition which at the time was thought to be poliomyelitis. At the age of 21, a similar attack, with right hemiplegia and a bloody cerebrospinal fluid, occurred. A diagnosis of congenital cerebral aneurysm was made. Five years later, at the age of 26, she was delivered at term by Caesarean section, although

22. de Carle, D. W.: Pregnancy and Cerebrovascular Complications, West. J. Surg. **57**:183-191 (May) 1949.

she had escaped a third subarachnoid hemorrhage at that time. A tubal ligation was done at the same time. Later, encephalograms were said to have established the diagnosis of angioma of the meninges.

In addition to the three cases reported above, de Carle [22] found 15 more instances of subarachnoid hemorrhages, associated with eclampsia; four of the patients died as a result of intracranial hemorrhage. In discussing de Carle's report, Dr. W. B. Thompson remarked that he had met only three fatal instances of intracranial hemorrhage among 75,000 deliveries which were not associated with eclampsia. One of these hemorrhages resulted from rupture of an arteriosclerotic vessel; the second, from an embolism complicating endocarditis, and the third, from encephalomalacia. Participating in the same discussion, Dr. Floyd Bell reported the case of a woman aged 36 who went through her third pregnancy normally but died shortly after delivery of subarachnoid hemorrhage, which he believed was due to rupture of a congenital aneurysm. Bell also mentioned another case, that of a nontoxic patient who went into coma and was delivered of a living child by Caesarean section, while the mother was in a moribund condition. Autopsy of the patient later "showed an aneurysm in the right parietal region."

Gershenfeld and Savel,[23] in 1950, reported a case of spontaneous subarachnoid hemorrhage which occurred on the third postpartum day in a primipara aged 24. Her symptoms consisted of headache and lethargy, which were 24 hours developing and were never severe. She showed only moderate rigidity of the neck and Kernig's sign. The spinal fluid was bloody and displayed a pressure of 110 mm. of water. Only one lumbar puncture was done, as the patient's condition cleared up rapidly with bed rest. The authors stressed the point that continuous caudal anesthesia for labor and delivery resulted in complete absence of straining and exertion. They expressed the opinion that more extensive bleeding would have occurred had the patient been subjected to a longer labor and greater physical effort. They believed the hemorrhage resulted from rupture of a small congenital aneurysm.

Dahle,[24] in 1946, reviewed 100 cases of spontaneous subarachnoid hemorrhage, three of which were associated with pregnancy. He remarked that this condition occurs in connection with stress or strain and was of the belief that childbirth is important in that respect. His first patient, a woman aged 28, gave birth to twins after 15 hours of labor. The delivery was uneventful. He felt that her toxemia was due to edema and albuminuria. Her blood pressure was 165/110. Immediately after delivery she experienced a severe headache and became cyanotic and semicomatose. A few days later abducens paralysis and nuchal rigidity appeared. Six days post partum a lumbar puncture revealed "spinal fluid findings typical of subarachnoid hemorrhage." There gradually developed papilledema and left hemiparesis, and she died 11 days post partum. Permission for autopsy was refused. Since the patient never had convulsions, but had only pre-eclampsia, this case may be considered as illustrative of the danger of toxemia concealing an underlying vascular anomaly.

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23. Gershenfeld, D. B., and Savel, L. E.: Pregnancy Complicated by Subarachnoid Hemorrhage, J. M. Soc. New Jersey **47**:374-375 (Aug.) 1950.

24. Dahle, T. Svangerskap og s. k. spontan subaraknoid alblødning, Nord. med. tidskr. **11**:587-588 (March 15) 1946.

His second patient, a woman aged 39, had nausea and vomiting during the last trimester of pregnancy. In the eighth month, edema of the ankles and albuminuria appeared, together with blurring of vision. The night before admission she experienced severe headache. On admission her blood pressure was 190/105, and two hours later she suddenly lost consciousness and died, without going into labor. Lumbar puncture, carried out post mortem, revealed a bloody fluid. Permission for autopsy was refused.

His third patient, a woman aged 34, delivered spontaneously at term. She had been a victim of migraine and had onset of headache before delivery. Convulsions occurred six hours after delivery; her blood pressure registered 90/50 when she dropped into coma. Later, she aroused, became restless, and complained of headache and stiffness of the neck. Six days later lumbar puncture showed xanthochromic fluid, which cleared within a week, and she made an uneventful recovery.

Stroink,[25] in 1936, discussed subarachnoid hemorrhage in connection with pregnancy and reported two cases. However, both the patients were thought to have eclampsia. In each instance the patient had sudden spontaneous subarachnoid hemorrhage, and on each occasion the mother survived.

Ramstad,[26] in 1948, reported the case of a woman aged 37, with two previous pregnancies, who had been well until the 37th week of her third pregnancy. The blood pressure and urine had been normal throughout her gestation. On admission to the hospital, she complained of pain in her neck, headache, and nausea. Four hours later she suddenly lost consciousness and showed intermittent Cheyne-Stokes breathing. The right pupil was twice as large as the left; both reacted equally to light. The eyegrounds were normal. There were slight twitching of her right arm and questionable stiffness of the neck. Her blood pressure registered 120/80; the urine was normal, and there were no signs of eclampsia. Lumbar puncture showed grossly bloody fluid. During the next few hours, without her going into labor, her condition became rapidly worse. A living infant was delivered by Caesarean section without anesthesia, the mother dying shortly after the operation. The author emphasized that the possibility of spontaneous subarachnoid hemorrhage must be borne in mind in the case of a patient who goes into noneclamptic coma during pregnancy.

TIME OF HEMORRHAGE

One might reasonably hold that spontaneous subarachnoid hemorrhage would occur during the height of labor. We have not found this to be true, either in our own experience or from perusal of cases reported in the literature; in fact, only in four of 28 cases did hemorrhage occur during the throes of labor. In 14 instances the patient had a prepartum hemorrhage. The earliest prepartum hemorrhage, as cited by Rhoads,[3] appeared in the third month of pregnancy. The patient had already survived three earlier hemorrhages—13, 2, and 1 year previously. She weathered an additional hemorrhage in her third month, but died of another hemorrhage, occurring in her fifth month, from a ruptured aneurysm of the circle of Willis. In another case, reported by Richardson and Hyland,[2] death resulted from a ruptured

25. Stroink, J. A.: Over subarachnoidale bloedingen in verband met zwangerschap, Nederl. tijdschr. verlosk. en gynaec. **39**:240-251, 1936.

26. Ramstad, H. H.: Spontan subaraknoidalblødning ved graviditet, Nord. med. **38**:888-889 (April 30) 1948.

TABLE 2.—*Summary of Noneclamptic Cases from the Literature*

Case	Age	Parity	Blood Pressure	Time of Hemorrhage	Source of Hemorrhage	Character of C. S. F.	Condition of Child	Mode of Delivery	Condition of Mother
Russell,[12] 1933	34	Not stated	?	8 hr. post partum	Undetermined	Grossly bloody	Normal, living	Spontaneous	Died; no autopsy
Ohler and Hurwitz,[10] 1932	27	Not stated	140/90	17 days post partum	Undetermined	Grossly bloody	?	Spontaneous	Died; no autopsy
de Carle,[22] 1949									
Case 1	29	Multipara	120/90	9 mo.	Aneurysm, left posterior communicating artery	Grossly bloody	Normal, living	Caesarean	Died; autopsy
Case 2*	23	Primipara	140/80	8 mo.	Aneurysm of ant. communicating artery	Grossly bloody	Normal, living	Caesarean	Died; autopsy
Moskowitz and Schneider,[16] 1938									
Case 1	25	Primipara	140/100	During labor	Probable aneurysm of pons	No spinal fluid	Undelivered	Undelivered	Died; autopsy
Case 2	26	Multipara	130/90	2 hr. post partum	Undetermined	Grossly bloody	Normal, living	Spontaneous	Recovered
Case 3	25	Primipara	110/80	Immediately post partum	Undetermined	Grossly bloody	Normal, living	Spontaneous	Died; no autopsy
Gershenfeld and Savel,[23] 1950	24	Primipara	?	3d day post partum	Undetermined	Grossly bloody	Normal, living	Spontaneous	Recovered
Rhoads,[3] 1947									
Case 1	Not stated	Primipara	210/180	3 and 5 mo. with previous hemorrhage	Aneurysm of Circle of Willis	Grossly bloody	Undelivered	Undelivered	Died
Case 2	27	Not stated	130/80	9 days post partum	Undetermined	Grossly bloody	Normal, living	Spontaneous	Recovered
Flexner and Schneider,[17] 1938	20	Primipara	Not stated	2 wk. post partum	? Following epinephrine	Grossly bloody	Normal, living	Low forceps	Recovered
Paucot and Gellé,[18] 1938	43	Multipara (XIV)	Not stated	3d trimester	Left lateral ventricle (syphilitic)	Grossly bloody	Dead; post-mortem Caesarean	Postmortem Caesarean	Died; autopsy
Olivecrona and Riives,[18] 1948	29	Not stated	Not stated	7 mo. pregnant	Arteriovenous aneurysm of left middle cerebral artery (by angiography)	Grossly bloody	Not stated	Not stated	Hemiplegic after removal of aneurysm
Strauss and Tarachow,[15] 1937	24	Not stated	120/70	9 mo., with two previous hemorrhages	Undetermined	Grossly bloody	Not stated	Not stated	Recovered
Dahle,[24] 1946	34	Not stated	90/50	During labor	Undetermined	Xanthochromic	Not stated	Spontaneous	Recovered
Garber and Maier,[4] 1948									
Case 1	26	Primipara	Normal	8 mo. pregnant	Undetermined	Grossly bloody	Normal, living	Spontaneous	Recovered
Case 2	26	Multipara	110/70	9 mo. pregnant	Undetermined	Grossly bloody	Normal, living	Spontaneous	Recovered
Case 3	24	Primipara	120/90	1 day post partum	Undetermined	Grossly bloody	Normal, living	Low forceps	Recovered
Richardson and Hyland,[2] 1941†	38	Multipara	195/120	4 mo. pregnant	Aneurysm, rt. internal carotid artery at junction with posterior communicating artery	Grossly bloody	Undelivered	Undelivered	Died; autopsy
Ramstad,[26] 1948	37	Multipara	120/80	8 mo. pregnant	Undetermined	Grossly bloody	Normal, living	Caesarean section	Died

* In de Carle's third case hemorrhage had occurred at ages of 10 and 21, but no hemorrhage occurred at time of delivery, at the age of 26.
† Two additional cases were mentioned by these authors, but not described.

aneurysm in her fourth month of pregnancy. The majority of hemorrhages happened during the second and third trimesters.

Of the 10 cases of postpartum hemorrhage, six occurred within the first 24 hours after delivery. The remaining four occurred on the 3d, 9th, 14th, and 17th postpartum days. The strain of labor may have been a factor in precipitating hemorrhage in the first six cases, and may even have been an exciting cause in starting the hemorrhage which occurred, in one case, on the third postpartum day. It is difficult, however, to believe that its association with the last four cases was anything more than fortuitous. We have been interested in observing that many of the patients in this category were able to withstand the physical demands of multiple pregnancies, only to have hemorrhage during a subsequent pregnancy, or years later, as observed by Sands [9] and Symonds.[8] The factors leading to the precipitation of spontaneous subarachnoid hemorrhages from aneurysms were well studied by Magee,[10] who found that in a series of 150 cases, 90% occurred while the patient was at rest. The findings of these authors, together with our own observations, lead one to ponder on the exact significance of labor in the production of such an intracranial catastrophe.

EVALUATION OF MATERIAL

The cases of 20 noneclamptic women in whom spontaneous subarachnoid hemorrhage developed were culled from the literature, as shown in Table 2. We have discovered 8 more cases, making a total of 28. Of the 28 patients, 12 were primiparas, and 10, multiparas, and the state of parity of 5 was not given. In 21 patients the source of hemorrhage was not determined. A ruptured aneurysm was the cause of hemorrhage in 6 patients, and in 1 bleeding was secondary to an angioma of the cerebellum. Nineteen infants lived; 5 died, and the fate of 4 was not stated. Fifteen mothers were delivered from below, and 7, by Caesarean section; 4 died undelivered, and the method of delivery of 2 was not stated. Twelve mothers (42.9%) died; of the 16 who survived, 2 had transient psychosis, and 2 were temporarily hemiplegic.

COMMENT

With the occurrence of spontaneous subarachnoid hemorrhage associated with pregnancy, it is imperative to determine whether or not toxemia is the causative factor in the bleeding. This is not always easy, but is most important when the signs of mild pre-eclampsia are present. Even with the various laboratory tests and other diagnostic aids at one's disposal, it is sometimes most difficult to distinguish between the eclamptic and the noneclamptic type. We have found that in attempting to evaluate reported cases, this problem was continually recurring, and we believe that the management of some of the patients might have been altered if a more definite method of diagnosis had been available.

In the presence of spontaneous subarachnoid hemorrhage, the patient's condition permitting, we believe that cerebral angiography is indicated. The optimum time for this procedure will depend on the total appraisal of the patient. As suggested by Wechsler and Gross,[27] the procedure may sometimes be carried out during the active hemorrhagic phase. Because it offers the only reliable means of demonstrating

27. Wechsler, I. S., and Gross, S. W.: Arteriography in Subarachnoid Hemorrhage, J. A. M. A. **136**:517-521 (Feb. 21) 1948.

the source of hemorrhage, we believe that angiography should be employed, especially when mild pre-eclampsia may suggest a toxic basis. In some cases elimination of the cause may be life-saving. The appropriate time and mode of treatment of an accessible aneurysm or vascular anomaly will depend upon the judgment of the neurosurgeon. At times it may be carried out as a lifesaving measure, regardless of the stage of pregnancy. Unless the actual source of hemorrhage is demonstrated, a conservative regimen, with absolute bed rest for several weeks, should be rigidly enforced.

The mode of delivery is the problem that faces the obstetrician. We agree with the majority of other authors that Caesarean section is the method of choice, as it obviates the strain of labor. Even though the majority of hemorrhages occurred before labor, it seems irrefutable that the physical efforts demanded by labor could well serve to precipitate a hemorrhage in a patient with a known vascular abnormality.

Some authors, such as Rhoads,[8] believe that in all cases of proved bleeding from intracranial aneurysm termination of pregnancy is justified. Others may agree with him that additional pregnancies should be prevented, preferably by sterilization, in women with a history of subarachnoid hemorrhage. We are of the opinion that future pregnancies would tend to place the patient in added jeopardy. The physician should recall the patients who succumbed to subarachnoid hemorrhage with the first demands of labor, as well as those who have passed successfully through multiple pregnancies. Rarely in medicine is a prognosis more difficult to render.

SUMMARY AND CONCLUSION

Twenty undoubted cases of spontaneous subarachnoid hemorrhage occurring in noneclamptic pregnancy are tabulated from the literature. Other cases associated with borderline eclampsia are mentioned but are not considered as strictly within this category. Eight new cases are contributed.

Contrary to our expectations, in only 4 cases (14.2%) did spontaneous subarachnoid hemorrhage occur during labor. In 14 cases (50%) it occurred prepartum and in 10 (35.8%) it occurred post partum. In 6 of the latter, it was within 24 hours after delivery.

The maternal mortality rate was 42.9%, including the eight new cases reported. The fetal mortality was 26.3%. However, in four instances no mention was made of the fate of the infant, which, if known, would necessarily alter this figure.

The diagnosis, management, and prognosis are discussed. We feel that all noneclamptic women, as well as those with borderline preeclampsia, who are victims of spontaneous subarachnoid hemorrhage should have the benefit of cerebral arteriography.

The condition of the patient permitting, accessible vascular lesions discovered by this method should be surgically explored.

EFFICACY OF AQUEOUS PENICILLIN ALONE AND COMBINED WITH OTHER MODES IN ADVANCED DEMENTIA PARALYTICA

A Five-Year Study

PHILIP N. BROWN, M.D.
YPSILANTI, MICH.

IN 1945 the use of amorphous penicillin was being suggested as a mode of treatment for syphilis of the central nervous system. A few articles had appeared indicating that the treatment had increased efficacy over the modes of therapy then in vogue, and it seemed desirable to check these impressions. Therefore, in September, 1945, an investigative project was set in motion at the Ypsilanti State Hospital. The patients with dementia paralytica committed to the hospital were suffering from the usual severe type. Criteria for the selection of patients in the groups to be studied were considered important. It was decided to divide the patients entering the hospital with dementia paralytica into five groups, taking them as nearly as possible in rotation. The criteria necessary for the patients to be considered were (1) that they not have had penicillin therapy prior to their admission to the hospital, and (2) that their physical status be such that they could tolerate therapeutic malaria if that mode of treatment was indicated in the group to which they were assigned. These criteria worked out satisfactorily during the early phases of the investigative procedure; but as time wore on the number of patients we admitted who had not received penicillin became smaller and smaller, and it was impossible to take patients in direct rotation as they entered the hospital. It was necessary, therefore, to select patients during a period of nearly four years before the five groups of 10 patients each could be collected.

At the time of initiation of this investigation, in 1945, amorphous water-soluble penicillin was all that there was available. Later, crystalline potassium-G penicillin was used. No criterion had been established as to the total number of units necessary in treatment of advanced syphilis of the central nervous system, nor had the unit dosage then been determined. My colleagues and I arbitrarily selected 4,000,000 units of penicillin as the optimum dose, dividing this into 200 injections of 20,000 units each every two hours for a period of 16 2/3 days. This penicillin was usually given as a solitary form of treatment, although rarely its administration coincided with a portion of the course of chemotherapy or with therapeutic malaria.

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PROCEDURE

There follows a description of the five groups and the mode of treatment carried out in each.

GROUP I: Four million units of penicillin in a dose of 20,000 units every two hours for 16⅔ days.

GROUP II: Four million units of penicillin given in the same manner as that in Group I, plus therapeutic malaria. The optimum course of therapeutic malaria was considered to be 50 hours at a temperature above 103 F. Either tertian or quartan malaria was used, depending on whether the patient was immune to tertian malaria. If he seemed so, he was inoculated with quartan malaria.

GROUP III: Four million units of penicillin in the mode described for Group I, plus one-year's treatment with intravenous injections of arsenic,[1] alternating with bismuth therapy.[2] This chemotherapy was given in courses of 10 injections in each series.

GROUP IV: Four million units of penicillin, a course of therapeutic malaria, and one year of chemotherapy, as described for Group III.

GROUP V: This group, which was used as a control, received a course of therapeutic malaria, plus chemotherapy in amounts noted for Group III.

It was hoped that after observation of these five groups the efficacy of penicillin alone or of penicillin combined with other means of treatment could be ascertained. It was recognized that these groups were relatively small for statistical purposes, but it was believed that at least an indication of the efficacy of the various modes of treatment could be gained.

As already mentioned, it took nearly four years to collect the 50 patients. In three instances, owing to technical errors, the patient had to be changed from one group to another; therefore, the exact size of the groups was not 10 each, as had initially been wished for. The numbers varied from nine to 12 for each of the five groups.

During the course of treatment of these patients, several complications were noted. In one of the patients receiving penicillin, a macular rash appeared, with mild elevation of temperature. Penicillin therapy was discontinued for a period of two days, then reinstituted, and carried on to termination of the course. No further difficulty was met with in this patient. In one patient exfoliative dermatitis developed after institution of penicillin therapy. Treatment was immediately discontinued, and the patient was removed from the group. No complications were noted during the course of therapeutic malaria. No deaths in the series were directly attributable to the treatment given.

Throughout the course of investigation of the patients, serological studies and detailed examinations of the spinal fluids were done. Specimens of blood and spinal fluid were taken for each patient every three to five months throughout the course of observation. Routine Kahn examinations were carried out on the blood; and, on the spinal fluid, quantitative Kahn determinations, cell counts, total-protein determinations, and Lange colloidal-gold studies were made.

RESULTS

Laboratory data on these 50 patients are voluminous and cannot be reported in detail. It may be said that our results corresponded closely with those reported by other workers, namely, that, despite any of the combined modes of treatment, the first element of the spinal fluid to show change was the cell count. This fell rather rapidly in all cases, and no particular indication as to the efficacy of one form of treatment over another could be noted in this respect. The second change which was more or less uniform was the rather rapid drop to normal in the total protein of the spinal fluid. The change next most significant was in the quantitative Kahn determination. The positivity of the reaction usually fell, but in some cases the fall

1. Oxophenarsine (mapharsen®) and tryparsamide.

2. Bismuth sodium thioglycollate (thio-bismol®) and bismuth sodium tartrate, given intramuscularly.

TABLE 1.—*Effects of Therapy on Laboratory Findings for the Five Treatment Groups*

Treatment Group	I		II		III		IV		V	
	Before	After	Before	After	Before	After	Before	After	Before	After
Mean quantitative Kahn reaction of CSF	80	31	144	51	139	53	140	88	98	29
Mean white cell count of CSF	46	4	35	5	79	6	44	12	39	3
Mean total protein of CSF	80	34	65	28	91	44	77	45	56	35
Blood Kahn reaction	+	+	+	+	+	+	+	±	+	+
Mean colloidal-gold curve	5554432110	2344321000	5555543210	4443221000	4444432100	4434321000	5555432100	3333320000	5554443100	2222210000
Mean months of treatments	27		21.2		21.4		19.3		28.2	

did not follow the clinical course of the patient in any respect. The colloidal-gold curve showed no correlation, either with the mode of treatment used or with the clinical progress of the patient, and in my opinion is useless as a prognostic sign with this disease. The serological reactions of the blood did not change notably with any form of treatment, remaining rather routinely positive. It must be remembered that the patients used in this series had long-standing, severe, untreated dementia paralytica, many of the patients being rather dilapidated before admission to the hospital.

In order that the voluminous laboratory data for the patients might be summarized concisely, some method of obtaining the mean had to be worked out. The five groups were taken as entities, and mean evaluations for colloidal-gold-curve figures, quantitative Kahn reactions, number of white cells per cubic millimeter of spinal fluid, and number of milligrams of total protein per 100 cc. of spinal fluid were obtained before, and then after, completion of treatment. The mean number of months the individual group was under treatment was also noted. These data are shown in Table 1.

Table 2 indicates the results of the various forms of treatment with respect to the ultimate outcome in each case. It should be noted that fine evaluations, in terms of

TABLE 2.—*Evaluation of Treatment with Respect to Ultimate Outcome for Each Treatment Group*

Treatment Group	No. Remaining in Hospital	No. Out of Hospital One Year	No. Dead
I	6	3	1
II	2	8	1
III	4	5	1
IV	5	5	2
V	7	0	2

degrees of improvement, were not made in this series. The only three considerations used were as follows: 1. Did the patient remain in the hospital? 2. Did the patient recover from his mental illness to such a degree that he was able to leave the hospital and remain out of the hospital at least one year? 3. Did the patient die? It is felt that the data in Table 2 strikingly point to one of the methods of treatment as outstanding among the five so far as these three criteria are concerned.

Because the electroencephalographic laboratory was not available at the time the study began, it was impossible to obtain electroencephalographic tracings on these patients before and after treatment. Tracings, however, carried out on 25 of the patients after completion of the treatment revealed that only 3 had electroencephalograms within normal limits, 4 had borderline-abnormal tracings, and 18 had definitely abnormal tracings. It is interesting to note that of the seven patients who had either normal or borderline abnormal tracings, only two were able to leave the hospital.

SUMMARY AND CONCLUSIONS

The results of a five-year investigation of five modes of treatment of state-hospital patients with severe dementia paralytica are presented.

It would seem from this study that for the severe type of dementia paralytica seen customarily in the state hospitals that penicillin combined with therapeutic malaria is the most desirable form of treatment.

Because the patients of both Groups II and IV received penicillin and therapeutic malaria, the only difference being that in Group IV the patients, in addition, received chemotherapy, the efficacy of the treatment for Groups II and IV should be relatively the same. This did not prove to be the case. It may be assumed, therefore, that at least in some cases of dementia paralytica chemotherapy has a deleterious effect on the course of the disease.

Electroencephalographic studies carried out on some of the patients during the later months of treatment are recorded, but the electroencephalograms are not thought to be an adequate criterion of either the desirability or the undesirability of any of the five methods of treatment.

Ypsilanti State Hospital.

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CRYPTOCOCCUS MENINGITIS (TORULOSIS) TREATED WITH A NEW ANTIBIOTIC, ACTIDIONE*

HENRY M. WILSON, M.D.
AND
ARTHUR W. DURYEA, M.D.*
ALEXANDRIA, LA.

THERE is no accepted effective therapy for Cryptococcus meningitis. Patients are treated empirically, and the results are poor. The present paper is the report of a case in which the relatively new antibiotic, actidione,* was used, with gratifying results. Experiments with other therapeutic agents and a second case of the disease treated unsuccessfully by the conventional methods are included.

This infection is caused by a fungus popularly known as Torula histolytica and so named in 1916 by Stoddard and Cutler,[1] who believed that cysts were caused in the host's tissues by the histolytic action of the fungus. Actually, the "cysts" were masses of the fungi with their capsules. Mycologists now properly call the organism Cryptococcus neoformans.[2] The infection caused by this fungus is cryptococcosis.

REPORT OF CASES

A white man aged 39, a paper-mill worker, began to lose weight, strength, and energy in October, 1948. Vitamins afforded temporary improvement. In May, 1949, specimens of stool revealed Hymenolepis nana, and he was given five "crystal-like" tablets (caprokol®?). This single treatment was unsuccessful; so he was hospitalized the following month and given several liquid-containing capsules (Dryopteris felix-mas?). After he returned home, he complained of vertigo, frequent headaches, and nausea, which when associated with coughing resulted in vomiting. His wife then first noticed a change; as she described it: "He seemed vacant mentally, paid less attention to me and our three children except to become irritated by us, and cried easily without any reason." There were "two spells" in which "everything seemed to go dark"; he sought his wife's aid, but "he could not speak and his eyes stared." Each time he was helped to bed at once, remained conscious, but did not recall the episodes after a few hours. His wife had further noted a gradual personality change and said, "I wondered what had come over him."

On July 2, 1949, he was admitted to this hospital. He was vague about his illness and complained of vertigo, malaise, loss of weight, and generalized abdominal soreness and said he had been treated elsewhere for "tapeworms and a little malaria fever."

From the Medical Service, Veterans Administration Hospital.

* Now St. Louis Medical Area Section Chief, Medicine, Veterans Administration.

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He had been "a sickly child" until he was 3 years old but knew of no specific illnesses until he had malaria in 1941. In 1942 he became jaundiced after immunization for yellow fever (acute infectious hepatitis?). His military service was limited to 29 months, at Camp Claibourne, La., and 36 months at Fort Ord, Calif. Since his discharge from the Army, he had lived in Louisiana.

On admission he was weak, malnourished, slightly apprehensive, but rational and cooperative. His height was 65 in. (165 cm.); his weight, 111 lb. (50.3 kg.) (his average weight had been 140 lb.) (63.5 kg.). The temperature was 99 F.; the pulse rate, 88 a minute, and the respiration rate, 20 a minute. The blood pressure was 90/65 mm. Hg. The heart and lungs were normal. The spleen was tender and palpable 1 fingerbreadth below the costal margin. Scattered over both upper extremities were many pea-sized tumors, resembling neurofibromas. Otherwise, the findings on physical examination were within normal limits. The red blood cell count was 5,170,000; the hemoglobin, 15.6 gm. per 100 cc., and the white cell count, 19,750, with 77% neutrophils, 17% lymphocytes, 3% monocytes, 2% eosinophils and 1% basophils. The Cutler sedimentation rate was 20 mm. in one hour. The urine was normal, and the Kahn reaction of the blood was negative. Repeated blood smears failed to reveal malarial parasites. Feces showed H. nana. The initial examination of the spinal fluid revealed clear fluid under a pressure of 200 mm. of water, with a negative Queckenstedt sign. The count was 148 white cells per cubic millimeter, of which 23% were polymorphonuclear leucocytes and 77% lymphocytes. The sugar content was 40 mg., and the total protein 210 mg., per 100 cc. The Wassermann reaction was negative. The colloidol gold curve was 0123321000. Very few cells of C. neoformans were seen in an India-ink mount of the spinal-fluid sediment.[3] (The growth in cultures was subsequently positively identified as C. neoformans by Dr. Norman F. Conant, of Duke University.)

The many spinal-fluid examinations made during hospitalization may be summarized briefly: The pressure was always elevated. The cells were almost exclusively lymphocytes, and the count varied from 1 to 608 per cubic millimeter, but was usually about 100. Before therapy several smears and cultures showed C. neoformans. The sugar varied from 24 to 58 mg. per 100 cc. and was usually 30 mg. The protein content varied from 46 to 305 mg. per 100 cc. and was usually about 270 mg. The chlorides varied from 577 to 660 mg. per 100 cc. and was usually about 627 mg. The globulin was increased.

The roentgenogram of the chest on admission was not remarkable. On Sept. 23, 1949, a small highlight, suggesting a cavity, was noted at the tip of the left third rib. This was unchanged on Oct. 28 and Nov. 28. On the films taken Dec. 20, and monthly thereafter through March, 1951, no abnormality was noted, and the previously suggestive area had disappeared. Biopsy of several of the pea-sized lesions of the skin revealed only chronic inflammation.

The maximum temperature was 102 F. on July 21, 1949, while the general range was from 98 to 101 F. He became afebrile on Aug. 18, two days after use of actidione® was started, and remained afebrile thereafter. The pulse rate reached 140, and the respiration rate 28 per minute very early in the hospitalization, but have remained within normal limits since. The weight fell to 97 lb. (44 kg.) in September, 1949. He gained gradually thereafter, to weigh 140 lb. (63.5 kg.). Cryptococci were never recovered from the urine, blood, or sputum. The erythrocyte range was from 5,300,000 to 3,550,000, with hemoglobin readings of 15.6 and 10.3 gm., respectively, per 100 cc. The anemia was present when he was eating very poorly. The leucocyte range was from 19,750, on admission, to 5,500. The differential counts were essentially normal except for an eosinophilia, the count reaching 12% in December, 1949. The Cutler sedimentation rate reached 25 mm. in one hour late in the first month but remained about 12 mm. thereafter.

In the six-week period before actidione® therapy was started, the patient became confused, then irrational, plucked at his bed clothes, and had involuntary urination and a positive Babinski sign. His gait was ataxic and became progressively wide-based, until he was unable to walk or stand. His condition was worse each day.

Treatment and Course.—Conventional therapy was employed at first. During the three-week period in which he received sulfadiazine, with sodium bicarbonate, 1 gm. each every four hours; aureomycin, 250 mg. every six hours; penicillin, 100,000 units every four hours; chloramphenicol, 250 mg. every four hours, and saturated potassium iodide solution, in a dose increasing 1 drop daily from the initial 5 drops to 60 drops three times a day; cultures of the spinal fluid continued to yield C. neoformans.

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Actidione,® 20 mg. given intramuscularly and 20 mg. given intrathecally daily, was started Aug. 16, 1949. Culture of material taken that day yielded C. neoformans. A culture started two days later remained sterile for 30 days and was discarded as such, since this particular strain had always grown in less than a week. The other medications were gradually discontinued. On Aug. 31, intrathecal administration of actidione® was discontinued because of marked signs of cerebral irritation, which may have been from the drug, and its intravenous use, 40 mg. daily at bedtime, was begun. On Sept. 9 our supply of actidione® was exhausted. Spinal-fluid culture on Sept. 18 yielded the organism, despite administration of aureomycin daily and saturated potassium iodide solution 60 drops three times a day. On Sept. 27 these medications were discontinued. Two days later use of actidione,® 60 mg. daily intravenously, was resumed alone. Spinal fluid four days later was negative for the organisms, and repeated cultures remained sterile; so the patient was given a Christmas holiday at home without medication. He returned 10 lb. (4.5 kg.) heavier and clinically improved, but culture of the spinal fluid again yielded the organisms. Since actidione® had inhibited but not eradicated the infection, aureomycin, 500 mg. every six hours, was given as the only medicament, starting Jan. 17, 1950. A culture started then also yielded C. neoformans. Two cultures thereafter were sterile; so use of aureomycin was stopped on Feb. 9 for evaluation of its effects. Because of the seriousness of the disease, it was decided on Feb. 17 to resume aureomycin therapy while awaiting another shipment of actidione.® On March 6 while he was receiving aureomycin, a specimen of spinal fluid yielded a growth. Treatment with actidione® alone was resumed March 22, 40 mg. being given intravenously daily. The sample taken one week later remained sterile 30 days. Cultures thereafter remained sterile except for the one started May 31, which yielded the organisms, despite daily administration of actidione® since March 22.

Twenty milligrams of actidione® had been given intrathecally daily for 16 days early in the hospitalization. This route was resumed after the positive culture on May 31, in the belief that a greater concentration of the drug would be achieved in the spinal fluid, so that there would be a better chance of eradicating the foci responsible for the occasional positive culture. After two days of intrathecal administration, his speech became slurred and his gait again ataxic. Pronounced lethargy and mental depression were apparent, so that the intrathecal administration was discontinued. He improved gradually thereafter, but about three weeks elapsed before his condition returned to its previous asymptomatic state. We believe this reaction represented toxicity from the intrathecal use of actidione® rather than an extension of the disease process.

The drug was continued intravenously, and subsequent cultures remained sterile. In January, 1951, the patient weighed 140 lb.; he was afebrile, asymptomatic, and clinically well and was discharged.

Culture of a specimen of spinal fluid obtained March 26, 1951, was sterile without medication.

Case 2.—A white man aged 61, a druggist, had been hospitalized here twice previously. In 1939 he was treated for acute submaxillary lymphadenitis. In 1941 he also had acute adenitis of the right cervical lymph nodes, which healed promptly with surgical drainage. He remained well until January, 1949, when he became insidiously ill with an infection of the upper respiratory tract, characterized by general malaise, low-grade fever, productive cough, and pain in the neck and shoulders. Gradually he noted blurring of vision, diplopia, vertigo, and severe headaches. About Feb. 15, 1949, his family physician advised hospitalization for "nephritis."

He was admitted on March 4, 1949. Physical examination revealed a well-developed, somewhat obese white man, who appeared chronically ill. He was irritable but rational and oriented. There was no cervical lymphadenopathy or nuchal rigidity. Ophthalmoscopic examination showed severe papillitis and hypertensive retinopathy. Breath sounds were harsh over the entire left lung, especially over the lower lobe. The blood pressure was 170/130 mm. Hg. The peripheral blood vessels were sclerotic. Mixed hemorrhoids were present. Otherwise, the results of physical examination were within normal limits.

A roentgenogram of the chest on March 4 showed a normal heart. There was increased density of the base of the left lung, which appeared pneumonic. The right lung was clear. Reexamination on March 12 (Fig. 1) showed that the area of increased density had become fairly well circumscribed, measured 3.5 cm. in diameter, lay in the midzone on the left fourth intercostal space, and presented an irregular central rarefaction, like a loculated cavitation. Fungous infection was suggested. On April 29 this cavitation was larger and more loculated, but no new lesions had appeared.

Electrocardiograms showed only left-axis deviation and sinus tachycardia. In serial blood counts the erythrocyte count ranged from 4,600,000 to 3,880,000, with hemoglobin between 14.8 and 12.2 gm. Leucocytes ranged from 8,300 to 11,350, with essentially normal differential counts. There was no eosinophilia. Cutler sedimentation rates ranged from 12 to 24 mm. in one hour.

Bronchoscopic examination revealed a heavy white adherent membrane in the anterior superior portion of the left main-stem bronchus. Bronchial washings showed C. neoformans, both by direct smear and culture. Previously, smears and cultures of sputum had been positive. The organism was not recovered in repeated cultures of blood and urine.

The results of the 24 spinal fluid examinations may be summarized as follows: Lymphocytes were found exclusively, the number varying from 9 to 197 per cubic millimeter. C. neoformans was identified by India-ink smear, culture, and direct count. The pressure was always elevated,

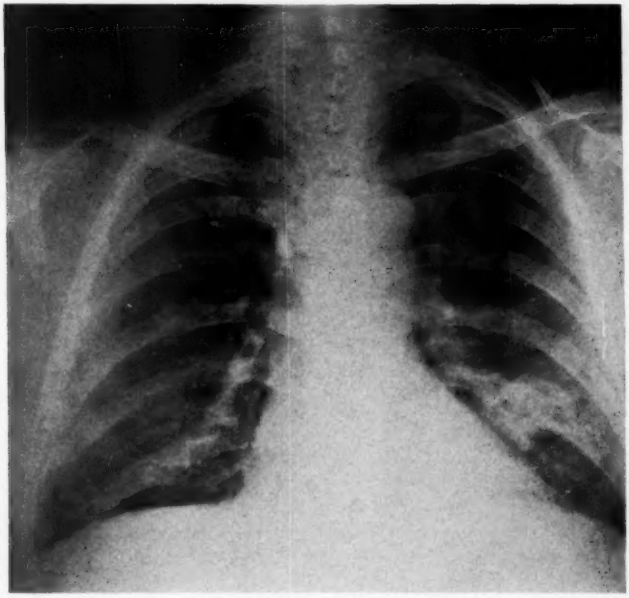

Fig. 1.—Posteroanterior view of the chest, taken March 12, 1949. Note the increased density in the midzone of the fourth left intercostal space and the irregular central rarefaction, suggesting loculated cavitation.

often above 600 mm. Sugar was low (5 to 25 mg. per 100 cc.), the protein elevated (265 to 625 mg. per 100 cc.), and globulin increased. Chlorides were reduced (594 mg. per 100 cc.).

The patient's course was steadily downhill. Disorientation, left hemiparesis, nuchal rigidity, involuntary urination, purpura, mania, and convulsions gradually developed. He died of respiratory failure on May 30, 1949.

Therapy included use of penicillin, sulfadiazine, streptomycin, potassium iodide, methylrosaniline chloride, sodium iodide, tripelennamine ("pyribenzamine") and sedatives, as required. Sodium iodide, 2 gm., was given intravenously several times. Streptomycin, 1 gm., was given intrathecally daily for several days. Parenteral alimentation was required the last two weeks. Temporary improvement in cerebral symptoms followed each reduction in spinal fluid pressure by lumbar tap.

At autopsy, the left pupil was observed to be markedly dilated and the eyeball protruded. The right lung weighed 400 gm. and was grossly normal. The left lung weighed 450 gm. In the middle portion of the lower lobe of the left lung there was a hard, irregular tumor mass. Section revealed that this was dark red and slightly necrotic and contained several small cavities. No caseation was visible, but pus exuded. The brain appeared wet. Its sinuses were engorged. The dura was adherent in the midportion of the longitudinal sinus. It was hyperemic but not definitely hemorrhagic. The left lateral ventricle contained a large amount of thick yellow fluid. Figure 3 shows the gross appearance of the many tumor-like aggregations of fungi and necrotic debris. Microscopic examination of the left lung showed masses of fungi. Sections of the brain

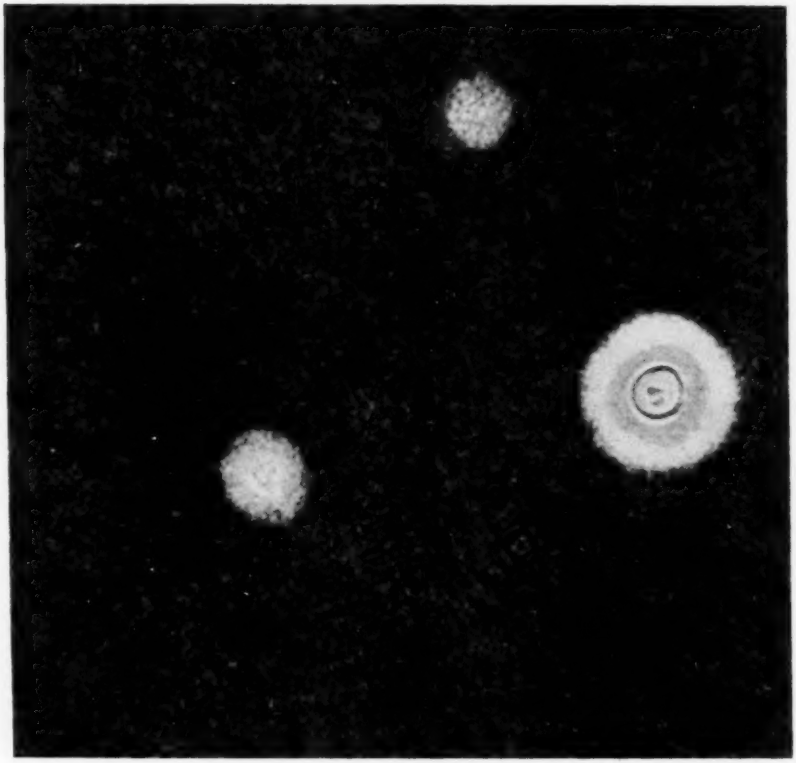

Fig. 2.—C. neoformans in centrifuged spinal fluid mixed with India ink.

(Fig. 4) revealed large areas of edema, engorgement of blood vessels, and massive infiltration with lymphocytes. There were several large cyst-like formations filled with a few lymphocytes, necrotic debris, an occasional polymorphonuclear leucocyte, and numerous circular vegetative fungi. Each had a thick capsule and a spore-like, dark-staining body lying eccentrically just beneath the capsule.

Comment.—It was impossible to ascertain whether the cervical adenitis in 1939 and the abscess drained in 1941 were caused by C. neoformans, and whether such could have been the original portal of entry.

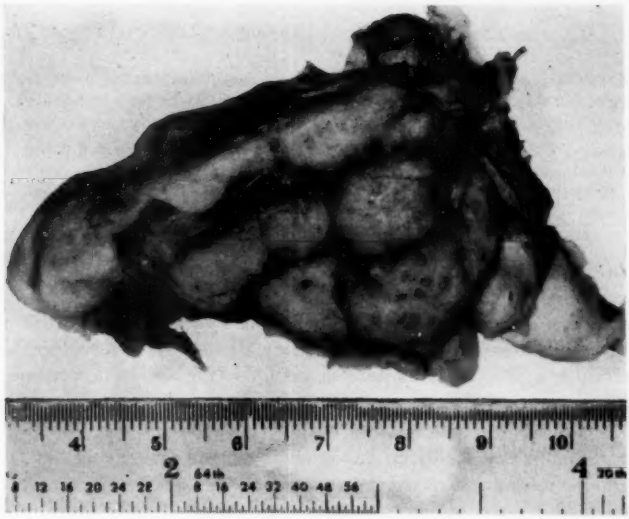

Fig. 3.—A portion of the brain, showing the gross appearance of the multiple tumor-like aggregations of fungi and necrotic debris.

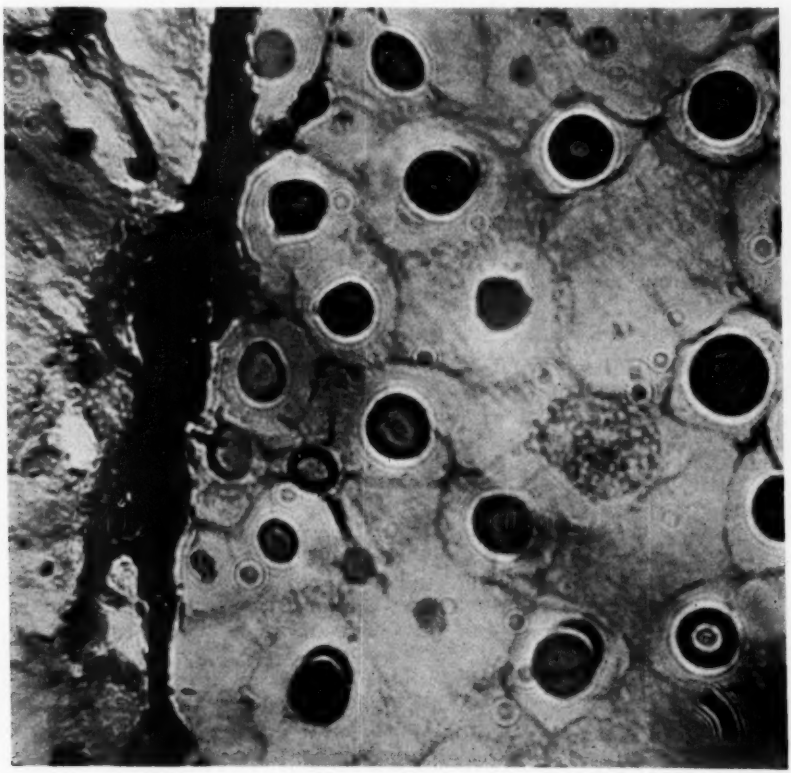

Fig. 4.—A section of the cerebrum, showing C. neoformans.

A sample of spinal fluid grew luxuriant colonies of C. neoformans in the presence of penicillin in all dilutions of from 1 to 20 units. Growth in streptomycin in dilutions of from 5 to 80 γ did occur but was delayed 24 to 48 hours, and was less abundant than that in the control.

Cryptococci were so numerous in the spinal fluid that they could be counted with ease as part of the differential cell count. That they were not misinterpreted blood cells was proved by India-ink mount, culture, and autopsy.

CHARACTERISTICS OF THE ORGANISM

Both in tissues and in culture mediums, C. neoformans is a thick-walled, oval to spherical, budding cell, 5 to 15 μ in diameter. The cells are surrounded by a wide gelatinous capsule, the width of which may equal or exceed the diameter of the cell itself. Identification is facilitated by emulsifying cerebrospinal fluid or other material in a drop of India ink [3] under a cover glass. The presence of the large gelatinous capsule, clearly seen with "high-dry" magnification in such preparations, differentiates this fungus from all other yeastlike organisms.[2]

The organism grows readily on Sabouraud's glucose agar, as well as on all the usual laboratory mediums at room temperature and at 37 C. In primary cultures from spinal fluid, blood, sputum, or tissue, the colonies usually appear in two to four days; however, recently Smith [4] has advised holding cultures for 30 days before discarding them as sterile.

Cryptococci are widely distributed in nature and have been found in wasps' nests; on the bodies of insects, stems of grasses, and plants, and in canned butter and milk. They have been demonstrated both on normal skin and on skin diseased from causes other than the fungus.[5] Cutaneous lesions have been present in many fatal cases of cryptococcosis, but organisms have rarely been demonstrated in these lesions.[6] Laboratory mice, guinea pigs, monkeys, and rabbits can be infected, but mice are the most susceptible.[7]

DIAGNOSIS

Obviously, the diagnosis of cryptococcosis is established once C. neoformans has been recovered. No diagnostic serologic test is available. In the 200 or so cases reported in the literature, the diagnosis has usually been made at autopsy. This has been so because the symptoms and signs in this infection do not form a pathognomonic constellation. The onset of the disease is difficult to date with certainty. The portal of entry and the method of spread are usually a mystery. Infection of the central nervous system caused 11 of Cox and Tolhurst's 12 patients to seek medical advice, and this "had submerged by its gravity, symptoms which might have arisen from the involvement of other organs."

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Early in the clinical course of cryptococcosis, a diagnosis of tuberculous meningitis is often entertained because of the dominant meningeal signs and symptoms; the pleocytosis, increased protein, decreased chloride, and decreased sugar in the spinal fluid, and the subacute or chronic course.[8] Lymphocytic choriomeningitis, various types of encephalitis, and syphilis are often considered. The colloidal gold curve may show a midzone rise or may be paretic in type. Interruption in the flow and reabsorption of cerebrospinal fluid may produce signs of increased intracranial tension, giving rise to the diagnosis of an expanding cerebral lesion. Several patients have undergone exploratory craniotomy,[9] and in rare instances localized granulomas have been uncovered.[10]

The course of the disease may be fulminating or chronic. Levin [11] reported a case with a course lasting less than one month. He found only nine of 60 cases reported up to that time in which the course exceeded a year. In 1948, a white girl, aged 15, was alive (but not well) after nine years of proved existence of the disease.[12] In the majority of cases reported death has followed within six months of the onset of definite meningoencephalitis.

In 1930 Freeman [13] classified cryptococcic infections of the central nervous system as follows:

1. A purely meningeal form, which was always present, and sometimes existed alone, causing a diffuse or granulomatous meningitis.

2. A perivascular form, which was frequently concomitant, probably representing a direct sequel to the meningeal disease, with invasion of the neural parenchyma oftenest along the perivascular sheaths from the meninges inward.

3. An embolic form, with lesions variable in size and number occupying the white matter, the basal ganglia and the cerebellum particularly, but in some cases present in great profusion in the cerebral cortex. This form probably explains deep-seated discrete lesions in the periventricular gray matter and in the tissues about the aqueduct.

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8. Magarey, F. R., and Denton, P. H.: Torula Histolytica Infection of Central Nervous System, Brit. M. J. **1**:1082-1083 (June 5) 1948.

9. (*a*) Cox and Tolhurst.[6] (*b*) Globus, J. H.; Gang, K. M., and Bergman, P. S.: Torula Meningo-Encephalitis, J. Mt. Sinai Hosp. **16**:14-34 (May-June) 1949. (*c*) Martin, J., and Padberg, F.: Torulosis of the Brain, Arch. Neurol. & Psychiat. **62**:679-680 (Nov.) 1949. (*d*) Prezyna, A. P.: Cryptococcus Neoformans Meningo-Encephalitis: Report of a Fatal Case, U. S. Armed Forces M. J. **1**:866-873 (Aug.) 1950.

10. (*a*) Daniel, P. M.; Schiller, F., and Vollum, R. L.: Torulosis of the Central Nervous System: Report of 2 Cases, Lancet **1**:53-56 (Jan. 8) 1949. (*b*) Krainer, L.; Small, J. M.; Hewlitt, A. B., and Deness, T.: A Case of Systemic Torula Infection with Tumor Formation in the Meninges, J. Neurol., Neurosurg. & Psychiat. **9**:158-162 (Oct.) 1946. (*c*) Swanson, H. S., and Smith, W. A.: Torula Granuloma Simulating Cerebral Tumor: Report of 2 Cases, Arch. Neurol. & Psychiat. **51**:426-431 (May) 1944.

11. Levin, E. A.: Torula Infection of the Central Nervous System, Arch. Int. Med. **59**:667-684 (April) 1937.

12. (*a*) Reeves, D. L.; Butt, E. M., and Hammack, R. W.: Torula Infection of the Lungs and Central Nervous System: Report of 6 Cases with Three Autopsies, Arch. Int. Med. **68**:57-79 (July) 1941. (*b*) Reilly, E. B., and Artman, E. L.: Cryptococcosis: Report of a Case and Experimental Studies, ibid. **81**:1-8 (Jan.) 1948.

13. Freeman, W.: Torula Meningo-Encephalitis, Tr. Am. Neurol. A. **56**:203-217, 1930.

Patients with cryptococcic infection of the central nervous system complain of headache, of any type, vomiting, and weakness. There may be prolonged remissions in the headache.[14] Confusion, irritability, and a change in gait are commonly noted by the patient's family. The reflexes, both deep and superficial, may be abnormal. The cranial nerves may be involved in nonspecific patterns. Invasion of the spinal cord is unusual. Papilledema is frequently present,[15] and optic nerve atrophy, less commonly.[12a] Convulsions and coma are late manifestations. Death is from respiratory failure.

Extraneural invasion is most frequent in the lungs.[16] Most authors believe there is nothing typical about the x-ray configuration. Diffuse or localized lesions may be seen.

TREATMENT

No specific therapy has been found for cryptococcosis. A wide variety of treatments has been reported. Surgical excision of localized lesions ("torulomas") has been of benefit.[17] Deep x-ray therapy has relieved headaches and caused shrinking of lymph nodes[9b] and subcutaneous tumors. Sulfonamides of all types and combinations have been used, without consistent results.[18] Penicillin has been widely employed,[19] despite Harford's report[20] that it is not effective in this disease. In one fatal case 65 million units of penicillin was given in five months.[9d] Potassium iodide has been used empirically.[21] Smith[4] reported two cases of chronic cryptococcus meningitis complicated by bone lesions and sensitive to an autogenous vaccine in which improvement followed desensitization and administration of sulfadiazine and potassium iodide. Cox and Tolhurst used vaccines and sulfapyridine. Methylrosaniline has been effective in vitro.[22] Quinacrine hydrochloride (atabrine®) in vitro was both fungistatic and fungicidal, but the required concentrations were well above toxic levels in vivo.[18i] Kligman and Weidman[7] suggested the use of

14. Marshall, M., and Teed, R. W.: Torula Histolytica Meningo-Encephalitis: Recovery Following Bilateral Mastoidectomy and Sulfonamide Therapy, J. A. M. A. **120**:527-529 (Oct. 17) 1942.

15. Stoddard and Cutler,[1] Cox and Tolhurst,[6] Levin.[11]

16. Cox and Tolhurst.[6] Greening, R. R., and Menville, L. J.: Roentgen Findings in Torulosis; Report of 4 Cases, Radiology **48**:381-388 (April) 1947.

17. (*a*) Daniel, Schiller, and Vollum.[10a] (*b*) Swanson and Smith.[10c] (*c*) Reeves, Butt, and Hammack.[12a] (*d*) Fisher, A. M.: The Clinical Picture Associated with Infections Due to Cryptococcus Neoformans (Torula Histolytica): Report of 3 Cases with Some Experimental Studies, Bull. Johns Hopkins Hosp. **86**:383-414 (June) 1950.

18. (*a*) Smith.[4] (*b*) Cox and Tolhurst.[6] (*c*) Kligman and Weidman.[7] (*d*) Daniel, Schiller, and Vollum.[10a] (*e*) Marshall and Teed.[14] (*f*) Fisher.[17d] (*g*) Haspel, R.; Baker, J., and Moore, M. B., Jr.: Disseminated Cryptococcus Neoformans, New Orleans M. & S. J. **101**:573-575 (June) 1949. (*h*) Mosberg, W. H., Jr., and Arnold, J. G., Jr.: Torulosis of Central Nervous System: Review of Literature and Report of 5 Cases, Ann. Int. Med. **32**:1153-1183 (June) 1950. (*i*) Voyles, G. Q., and Beck, E. M.: Systemic Infection Due to Torula Histolytica (Cryptococcus Hominis): Report of 4 Cases and Review of Literature, Arch. Int. Med. **77**:504-515 (May) 1946.

19. Prezyna.[9d] Haspel, Baker, and Moore.[18g] Mosberg and Arnold.[18h] Voyles and Beck.[18i]

20. Harford, C. G.; Martin, S. P.; Hageman, P. O., and Wood, W. B., Jr.: Treatment of Staphylococcic, Pneumococcic, Gonococcic and Other Infections with Penicillin, J. A. M. A. **127**:325-329 (Feb. 10) 1945.

21. Smith.[4] Voyles and Beck.[18i]

22. Daniel, Schiller, and Vollum.[10a] Voyles and Beck.[18i]

artificial fever after they noted improvement in the spinal fluid of a patient following bouts of fever from his coincidental malaria. They found that cryptococci are inhibited by 40 C. and die after six days at this temperature. Mosberg and Arnold [18h] were unable to maintain artificial fever long enough for evaluation. They achieved some improvement by extreme alkalization therapy in two cases. Globus [9b] reported no consistent benefit from arsenicals, antimony potassium tartrate, colloidal copper, quinine, merbromin, tricresol, methanamine, acriflavine, streptomycin and gold sodium thiosulfate. Colloidal silver, sulfadiazine,[18h] nitrofurazone (furacin®), glucosulfone sulfone (promin®), thymol,[18l] and tyrocidine fall into the same category.

Daniel [10a] emphasized that the fungus in vivo has a thick capsule, which it loses on culture, thereby becoming more susceptible to many agents. Fisher [17d] stressed that any chemotherapeutic agent, to be effective in either the generalized or the meningoencephalitic form, will have to be one capable of a high degree of diffusibility in order to penetrate the cyst-like collections of cryptococci in the tissues and/or one capable of destroying the capsules, and thereby rendering the organisms more susceptible to destruction by the host.

In 1946 certain streptomycin-producing beers of S. griseus were found to contain an agent which inhibited the growth of C. neoformans.[23] This antifungal antibiotic was named actidione,® since it appeared to be a diketone produced by an actinomycete. Subsequent work simplified its formula [24] to $C_{15}H_{23}NO_4$—containing one hydroxyl and only one ketone group. Crystalline actidione® inhibited C. neoformans in concentrations as low as 0.0002 mg. per milliliter in vitro. This high order of activity suggested its special usefulness in the treatment of cryptococcosis.

Haspel and associates [18g] used actidione® in the case of a white woman aged 58 who had been ill one year. In vitro the organism was inhibited by a concentration of 1 : 100,000. Treatment was begun with 20 mg. intramuscularly daily, and two days later the dose was increased to 40 mg. She seemed to improve clinically but died 20 days after the initiation of treatment. Cultures of the blood and spinal fluid taken at autopsy yielded C. neoformans. The brain, spinal cord, meninges, pericardium, kidneys, adrenals, and lungs showed diffuse involvement. Kligman and Weidman found actidione® effective in vitro but not in vivo. In mouse therapeutic tests Fisher found propamidine (4,4′-diamidinodiphenoxy propane dihydrochloride), aureomycin, penicillin, streptomycin, and actidione® to be of little value, although he suggested some fungicidal effect of actidione® in vivo provided the drug could be brought in direct contact with the fungi.

IN VITRO EXPERIMENTS

The in vitro effect of various bacteriostatic agents on the growth of C. neoformans isolated in Case 1 was studied. Briefly, these experiments revealed that growth of this particular strain was inhibited for the full 12-day test period by the following agents: aureomycin, 5 γ per cubic centimeter; actidione,® 0.05 mg. per cubic centimeter, and methylrosaniline chloride, 1 : 200,000. The controls yielded growth in two to three days. It is also noteworthy that chloramphenicol in 2.5, 5, and 10 γ per cubic centimeter had no inhibitory effect; growth occurred as rapidly as in the

23. Whiffen, A. J.: The Production, Assay and Antibiotic Activity of Actidione, an Antibiotic from Streptomyces Griseus, J. Bact. **56**:283-291 (Sept.) 1948.

24. Kornfeld, E. C., and Jones, R. G.: The Structure of Actidione, an Antibiotic from S. Griseus, Science **108**:437-438 (Oct. 22) 1948.

control. Penicillin, in increasing concentrations from 5 units per cubic centimeter, and sulfadiazine, in increasing concentrations from 5 mg. per 100 cc., suppressed growth for six days. No greater effect was obtained from the combination of penicillin and sulfadiazine.

The most noteworthy finding was inhibition of the fungus by the addition of spinal fluid from the patient receiving actidione* to the culture mediums. Spinal fluid from the first patient while receiving 60 mg. of actidione* intravenously daily completely inhibited the growth of that strain of C. neoformans for 14 days, at which time the medium was discarded as sterile. Concentrations of spinal fluid in the medium ranged from 2 to 40%. We were unable to determine the actual concentration of the drug itself in the patient's spinal fluid. This experiment proves that actidione* administered intravenously passes into the spinal fluid in fungistatic amounts.

General alkalization raising the pH of spinal fluid to 7.8 was recently reported as being beneficial.[18h] Cryptococci grew equally well in our laboratory in mediums the pH of which had been adjusted to 7.6, 8.0, and 8.4.

SUMMARY

Actidione* merits further investigation in the treatment of C. neoformans meningoencephalitis (torular meningitis). Actidione* is an antifungal antibiotic derived from the fermentation of S. griseus. Its empirical formula has been reported to be $C_{15}H_{23}NO_4$. It is toxic to man administered intrathecally but not when given intravenously or intramuscularly. Administered intravenously, actidione* passes into the cerebrospinal fluid in concentrations which are fungicidal for C. neoformans.

A patient is reported herein who was treated with actidione* and is asymptomatic, with sterile spinal fluid cultures 20 months after the diagnosis of cryptococcic meningoencephalitis was established. Another case, in which treatment was carried out earlier by conventional methods, is reported, with autopsy findings.

The diagnosis, course, and conventional ineffective therapy in cryptococcosis are discussed, with references to the literature.

In vitro experiments in our laboratory showed that actidione,* 0.05 mg. per cubic centimeter; aureomycin, 5 γ per cubic centimeter, and methylrosaniline chloride, 1:200,000, inhibited the growth of C. neoformans. Penicillin and sulfadiazine exhibited less suppression. Chloramphenicol, up to 10 γ per cubic centimeter, and alkalization to pH 8.4 had no effect.

Veterans Administration Hospital, Alexandria, La. (Dr. Wilson).
420 Locust St., St. Louis 2 (Dr. Duryea).

The actidione* used was supplied by H. F. Hailman, M.D., Ph.D., of the Upjohn Company, Kalamazoo, Mich.

The fungus studies were carried out by Frank Clifton, A.B.

ELECTROENCEPHALOGRAPHIC FINDINGS IN SPINAL CORD AND BRAIN STEM LESIONS

GERALD F. PERRY, M.D.
AND
DONALD J. SIMONS, M.D.
NEW YORK

TWO REPORTS on electroencephalographic studies in cases of lesions of the spinal cord have been published, with different results. Kaplan and Stearns [1] reported 15 cases, in all of which the electroencephalograms were abnormal. The abnormalities were not the same, but the paroxysmal nature of the abnormalities was common to all. These paroxysmal discharges were frequently localized over the central sagittal, and precentral areas. In explanation, the authors suggested that the abnormalities might be the result of antidromic volleys in the pyramidal tracts. On the other hand, Merlis and Watson [2] reported normal electroencephalographic findings in 16 of the 18 cases of cord injury which they had collected. These injuries had resulted in partial or complete anatomic or functional transection of the cord. In one case the abnormalities were accounted for by associated head injury. Accordingly, the present study was made to investigate the problem further and, if abnormalities were found in the electroencephalogram, to establish the cause.

METHOD

Twenty-six cases were selected which fulfilled the following conditions: (*a*) no history or clinical evidence of head trauma; (*b*) no neurologic dysfunction above the level of the neck except in the two cases with lesions in the brain stem, which were included to help in establishing a cause for the abnormalities; (*c*) bilateral involvement of the corticospinal tract, as shown by the bilateral Babinski toe sign and by hyperreflexia in the arms and legs.

The cases selected included degenerative, traumatic, and compressing lesions. All the lesions of the cord were in the cervical region except for a tumor at the third thoracic vertebra. The lesions in the brain stem were well localized. The table shows the grouping of these cases on an etiologic basis. The duration of the lesions ranged from four months to 10 years. In the majority of cases the symptoms indicated a duration of over a year.

OBSERVATIONS

It will be seen that of a total of 26 cases, abnormal electroencephalograms were found in only 9. Of these 9, the lesion could be accounted for in 4, as tongs were used to apply traction on the head and neck and the instrument invariably entered

From the Neurological and Neurosurgical Service (Cornell Division), Bellevue Hospital.

1. Kaplan, L. I., and Stearns, E.: Electroencephalographic Studies in Spinal Cord Disease, Arch. Neurol. & Psychiat. **62**:293 (Sept.) 1949.

2. Merlis, J. K., and Watson, C. W.: The Electroencephalogram After Injury to the Spinal Cord in Man, Arch. Neurol. & Psychiat. **61**:695 (June) 1949.

the inner table of the skull. The type of electroencephalographic abnormality so produced may be seen in the figure. In 2 other cases degenerative lesions of the cord were diagnosed as multiple sclerosis. The diagnosis was based on the history of exacerbations and remissions and on the presence of more than one lesion in the cord. The abnormalities could be attributed to cerebral involvement, although clinical signs were lacking. In another case the record had a single spike discharge, which was not repeated elsewhere and hence was considered an artifact.

Grouping of Twenty-Six Cases of Lesions of the Spinal Cord and Brain Stem with Electroencephalographic Studies on an Etiologic Basis

Group*		Etiologic Agent	Tracts and Gray Matter Involved	No. Cases	EEG Findings: Normal	EEG Findings: No.	EEG Findings: Abnormal Type
A							
	1	Osteoarthritis, cervical vertebrae, with bony spurring into spinal canal	Corticospinal, posterior column; anterior horn or roots; spinothalamic (2 cases)	5 (3 verified by operation)	3	1	Spiking in motor and motor parietal areas, more of the left side
						1	Case excluded; lesion result of application of tongs (figure)
	2	Anemia and/or achlorhydria (combined sclerosis)	Corticospinal, posterior columns	6	5	1	Notched waves 5 cps of moderate amplitude, bilateral, in anterior temporal-occipital leads; lower voltage 5 cps was in left central-anterior temporal lead
	3	Multiple sclerosis	Corticospinal, posterior columns	4	2	2	Case excluded because of cause of lesion
	4	Unknown	Corticospinal, anterior horn	3	2	1	Single spike in the whole record (artifact ?)
	5	Compressing lesion, tumor, I-V disk; fracture dislocation of vertebrae	Corticospinal, spinothalamic, posterior roots, (?) posterior column, anterior horn or root	6	3	3	Similar abnormality to that in figure; all patients had tongs applied for head traction
B							
	1	Degeneration	Corticospinal, corticobulbar, extrapyramidal, medial longitudinal fasciculus; cranial nerves III, IV, V, and VI; cerebellar tracts	1	1	0	
	2	Intrapontine	Corticospinal; sensory; cranial nerves V to VIII; vestibular; cerebellar	1 (verified by operation)	1	0	
			Total	26	17	9 (7 excluded)	

* Group A comprised spinal cord lesions; group B, brain stem lesions.

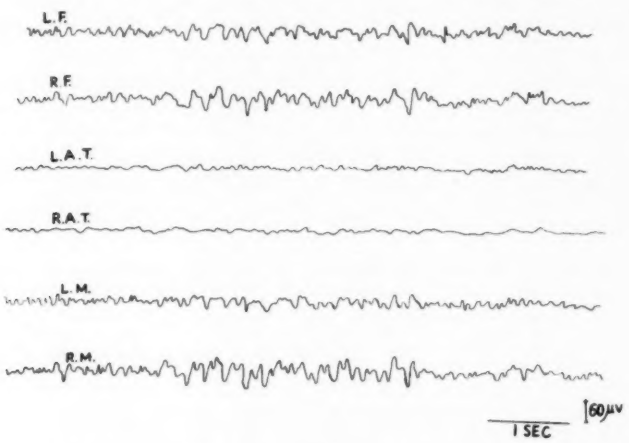
These seven cases being excluded for the reasons given, only two cases had unexplained abnormalities. Two abnormal electroencephalograms out of a total of 26 or 20 would be within the range of abnormalities found in the general population.[2a] This result is in agreement with the findings of Merlis and Watson and of Pacella and Jungeblut.[3] The latter studied the electroencephalograms of patients with residual paralysis from poliomyelitis. It cannot be gainsaid that the electroencephalograms in Kaplan's series were all abnormal, but no mention is made of previous head injuries, nor is it stated whether the patients had involve-

2a. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Electroencephalographic Classification of Epileptic Patients and Control Subjects, Arch. Neurol. & Psychiat. **50**:111 (Aug.) 1943.

3. Pacella, B. L., and Jungeblut, C. W.: The Electroencephalogram in Poliomyelitis, Arch. Neurol. & Psychiat. **58**:447 (Oct.) 1947.

ment of cranial functions in addition to their spinal cord lesions. Besides, no specific pattern was found common to all the cases.

Electroencephalographic changes may be explained theoretically, we think, on the basis either of antidromic volleys along the corticospinal tracts set up by chemical irritation at the site of the lesion, or of progressive degeneration upward along the uninterrupted axons forming the corticospinal tract, and thus resulting in ultimate degeneration of the parent cortical cell. For this reason, we selected lesions of the cervical portion of the cord and lesions of the brain stem having bilateral involvement of the corticospinal tract, as the proximity of the lesion to the cortex would presumably result in quicker and more effective changes in the cortical cells. These changes, chemical or degenerative, might or might not result in abnormal electrical activities which could be picked up by scalp electrodes placed over the motor area. Since no unexplained electroencephalographic abnormalities



Electroencephalographic abnormalities in a case of lesion of the brain stem of traumatic origin.

were found, it may be assumed that these changes, if present, were not sufficient to cause abnormal patterns in the electroencephalogram.

Stimulation of sensory pathways obviously mediated via the thalamus causes various changes in the electroencephalographic pattern. The patients in our study had both partial and severe involvement of the sensory tracts. The chemical stimulus either was not present or was of insufficient strength to produce changes in the electroencephalographic pattern. Changes in the quality of the alpha pattern were neither definite nor striking enough to warrant any conclusion.

SUMMARY

Electroencephalographic recordings were made on 24 subjects with lesions of the spinal cord and on 2 subjects with lesions of the brain stem. The patients with spinal cord lesions were selected from a larger group because they had no history of head trauma and no involvement of cerebral functions. All had bilateral lesions

of the corticospinal tract. Sensory tract involvement was also present in most of the cases.

Nine patients had abnormal electroencephalograms. In four the abnormalities could be explained by injury produced by tongs applied for traction on the head and neck. Two patients had multiple sclerosis, and the possibility of cerebral involvement could not be excluded. Only a single spike appeared in the whole record of one subject, and hence was considered an artifact. The abnormalities of two patients were unexplained. The incidence of abnormalities (namely, 10%) is roughly that of the expected percentage of abnormalities in the general population.

EFFECT OF POTASSIUM ON ELECTROCARDIOGRAPHIC ABNORMALITIES PRODUCED DURING INSULIN SHOCK

IRVIN A. KRAFT, M.D.
HERBERT SALZBERG, M.D.
AND
J. A. ROSENKRANTZ, M.D.
NEW YORK

DEVIATIONS from the normal electrocardiogram have been reported in schizophrenic patients in the course of insulin-shock therapy.[1] Thiamine deficiency [2]; hypoglycemia [3]; anoxia, with decreased blood flow through the coronary arteries,[4] and epinephrine release [5] have been implicated in these changes. Other investigators have demonstrated the occurrence of hypopotassemia in diabetic acidosis and in other clinical disorders and have described characteristic cardiovascular and electrocardiographic changes associated with decreased serum-potassium concentration.[6] Messinger [4] and Hadorn [1b] observed that the most frequent electro-

From the Neuropsychiatric and Medical Services, Veterans Administration Hospital, Bronx, N. Y.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. (*a*) Beiglbock, W., and Dussik, T.: Physiology of the Hypoglycemic Shock in Treatment of Schizophrenia, Am. J. Psychiat. (Supp.) **94**:50, 1938. (*b*) Hadorn, W.: Untersuchungen des Herzens im hypoglykämischen Schock: Das Elektrokardiogram bei der Kardiazolschockbehandlung der Schizophrenie, Arch. Kreislaufforsch. **2**:70, 1937.

2. Goldfarb, W., and Bowman, K. M.: Vitamin B1 Requirement During Insulin Shock Therapy, Am. J. Psychiat. **98**:393, 1941.

3. Kalinowsky, L. B., and Hoch, P. H.: Shock Treatments and Other Somatic Procedures in Psychiatry, New York, Grune & Stratton, Inc., 1949.

4. Messinger, E.: Cardiovascular Changes Associated with the Insulin Shock Treatment, Ann. Int. Med. **12**:853, 1938.

5. Gilbert, R. A., and Goldzieher, J. W.: Mechanism and Prevention of Cardiovascular Changes Due to Insulin, Ann. Int. Med. **25**:928, 1946.

6. (*a*) Atchley, D. W.; Loeb, R. F.; Richards, D. W., Jr.; Benedict, E. M., and Driscoll, M. E.: On Diabetic Acidosis: Detailed Study of Electrolyte Balances Following the Withdrawal and Reestablishment of Insulin Therapy, J. Clin. Invest. **12**:297, 1933. (*b*) Winkler, A. W.; Hoff, H. E., and Smith, P. K.: Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride, Am. J. Physiol. **124**:478, 1938. (*c*) Holler, J. W.: Potassium Deficiency Occurring During the Treatment of Diabetic Acidosis, J. A. M. A. **131**:1186 (Aug. 10) 1946. (*d*) Tarail, R.: Relation of Abnormalities in Concentration of Serum Potassium to Electrocardiographic Disturbances, Am. J. Med. **5**:828, 1948. (*e*) Danowski, T. S.; Peters, J. H.; Rathburn, J. C.; Quashnock, J. M., and Greenman, L.: Studies in Diabetic Acidosis and Coma, with Particular Emphasis on the

(Footnote continued on next page)

cardiographic abnormalities associated with hypoglycemia was a flattening or inversion of the T wave and sinus arrhythmia; other findings were a pathological Q wave in lead III, changes in R and S voltage, slight widening of the QRS complex, and appearance of U waves or auricular and ventricular extrasystoles. Bellet and his co-workers,[9h] found similar changes in pattern associated with hypopotassemia and classified these as follows: (1) depression of the S-T segment accompanied with lengthening of the Q-T interval; (2) inversion of the T wave and prolongation of the Q-T interval, frequently followed by a U wave (with inversion of the T wave there might be elevation of the initial portion of the S-T segment, followed by a downward dip, prolongation of the Q-T segment, or dipping of the inverted T wave below the isoelectric line); (3) upright T waves and prolonged Q-T interval, with the T wave occupying the entire Q-T segment; (4) T wave almost isoelectric and accompanied with a terminal U wave; (5) normal T wave followed by an unusual prominent U wave without prolongation of the Q-T interval.

The present investigation was undertaken in two phases: (1) to determine the effect of insulin-induced hypoglycemic shock upon the electrocardiographic tracings and serum-potassium concentration in schizophrenic patients, and (2) to observe whether the oral adminstration of potassium salts would protect against the development of alterations in the electrocardiogram and the serum-potassium level.

TABLE 1.—*Previous History of Insulin-Shock Therapy of Ten Schizophrenic Patients*

Patient	Previous No. of Insulin Injections	No. of Times Previously in Stage-1 Coma	No. of Times Previously in Stage-2 Coma
1	74	36	1
2	40	33	..
3	19	1 *	..
4	43	5	..
5	31	..	1
6	12	..	..
7	68	9	15 †
8	15	2	..
9	24	6	2
10 ‡	20	2	3

* Insulin dose increased to 1,240 units.
† Quiet type.
‡ One year prior to the present study the patient had received a complete series of over 100 insulin injections.

PROCEDURE

Ten young white men with schizophrenia who were undergoing routine insulin-shock therapy served as subjects for this investigation. Except for one patient, who was given regular amorphus insulin, the patients received regular crystalline insulin by intramuscular injection

Retention of Administered Potassium, J. Clin. Invest. **28**:1, 1949. (*f*) Nadler, C. S.; Bellet, S.; Reinhold, J. G., and Lanning, M.: Alterations in the Serum Potassium and Their Relation to Certain Constituents of the Blood in Diabetic Acidosis, Am. J. M. Sc. **218**:308, 1949. (*h*) Bellet, S.; Steiger, W. A.; Nadler, C. S., and Gazes, P. C.: Electrocardiographic Patterns in Hypopotassemia: Observations on 79 Patients, ibid. **219**:542, 1950. (*i*) Frenkel, M.; Groen, J., and Willebrands, A. F.: Low Serum Potassium Level During Recovery from Diabetic Coma, with Special Reference to Its Cardiovascular Manifestations, Arch. Int. Med. **80**:728 (Dec.) 1947. (*j*) Diefenbach, W. C. L.; Fisk, S. C., and Gilson, S. B.: Hypopotassemia Following Bilateral Ureterosigmoidostomy. New England J. Med. **244**:326, 1951.

in doses of from 160 to 720 U. S. P. insulin units. Each of the 10 patients had been on insulin-shock therapy for a period prior to the time of this study. Table 1 summarizes the previous insulin-shock history of each patient. Each had received successive increasing amounts of insulin before either stage-1 or stage-2 coma was effected. Stage 1 was defined as a light-coma or subcoma state, in which the patient would respond to painful stimuli. Stage 2 was that level at which a deeper coma was obtained, in which the patient failed to respond to external painful stimuli.

Only patients who exhibited effective insulin-coma reactions without convulsions were selected. This criterion was desirable in order that electrocardiographic artefacts and difficulty in interpreting changes in serum-potassium concentration might be avoided. The patients were in a controlled environment. Each received the same diet and observed the same bedtime curfew as the others, had no food prior to the intramuscular administration of insulin, at 6:30 a. m., and remained in the same room for his treatments. Seven patients were studied at least twice. A control serum-potassium determination was made and a control electrocardiogram taken before the injection of insulin. Subsequent to the administration of insulin, electrocardiograms were taken at approximately 15-minute intervals. When T-wave changes were demonstrated, blood samples were drawn for serum-potassium determinations. On the second day, at almost the same hour, the same procedure was followed, except that the patient received 10 gm. of potassium chloride in a glass of tomato juice simultaneously with the administration of insulin. Serum-potassium concentrations were determined by the flame-photometer technique; the electrocardiograms were obtained with a direct-writing portable electrocardiographic apparatus.

TABLE 2.—*Effect of Insulin Shock, With and Without Oral Administration of Potassium Chloride, on Electrocardiogram and Blood-Potassium Concentration in Ten Schizophrenic Patients*

	Serum Potassium, mEq./L			Electrocardiogram T-Wave Amplitude, Mm.		
Patient	Control	Shock	Shock with Oral KCl	Control	Shock	Shock with Oral KCl
1	2.87	2.37	5.5	2.5	0.5	4.5
2	3.25	4.0	...	3.8	2.0	...
3	3.25	2.65	...	2.2	1.0	...
4	2.5	....	5.75	1.0	0.2	1.5
5	3.75	....	4.35	1.4	0.6	1.2
6	5.50	4.85	6.25	3.1	1.0	1.8
7	3.92	3.57	5.43	1.5	0.9	3.0
8	4.15	3.21	5.38	2.0	0.5	3.2
9	5.15	4.31	4.3	2.2	0.2	4.0
10	3.95	4.26	5.38	2.4	2.3	3.9

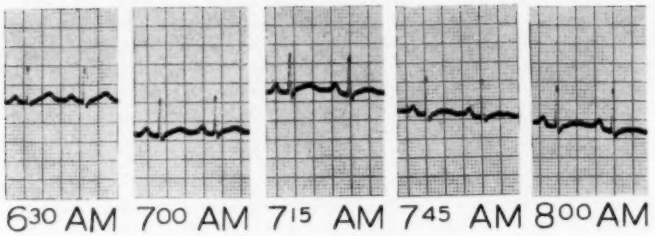
RESULTS

In Table 2 the results of the studies are outlined. While in shock all patients showed electrocardiographic changes, with flattening of the T waves. The extent of T-wave alterations varied with the patients. In addition, on six occasions the serum-potassium levels were reduced. When 10 gm. of potassium chloride was given orally, there was a subsequent rise in the serum-potassium levels, and with it a significant increase in the amplitude of the T waves (Fig.).

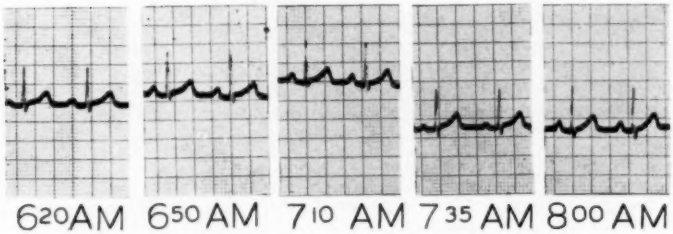
COMMENT

From our data it may be noted that there was no correlation between control serum-potassium levels and the number of insulin injections and/or stage-1 or stage-2 comas the patient experienced prior to this study. However, as compared with the normal range of serum-potassium concentrations of 3.5 to 5.0 mEq., in

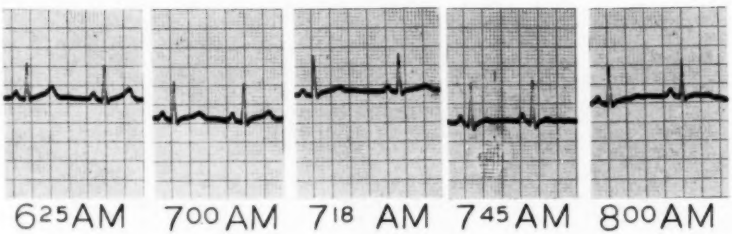
1a Insulin alone



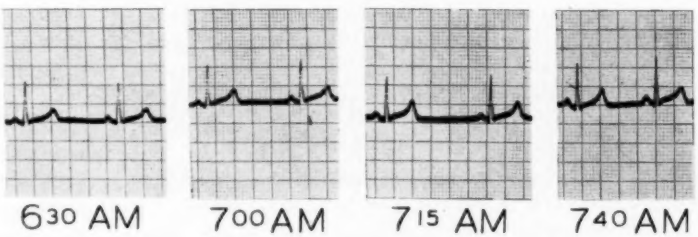
1b Insulin plus potassium



2a insulin alone



2b insulin plus potassium



Effect of potassium on electrocardiographic changes produced by insulin shock.

four of our control serum studies low, in two slightly elevated, and in four normal potassium levels were obtained. It would appear that the effect of prior insulin-shock therapy upon the control potassium levels was variable. However, repeated insulin therapy may have been responsible for the low serum-potassium concentration in some patients.

Under the conditions of this investigation, insulin (hypoglycemic) shock lowered the serum potassium in six of eight patients as compared with the control levels; the two other patients had a rise in serum-potassium concentration. Of interest is the fact that of those patients for whom a fall in potassium level was noted, in only one (case 8) did it drop to an abnormal level. The others either had had a lower than normal serum-potassium level at the onset or, if the level was higher than or within the normal range, the fall in serum potassium during shock therapy was still within normal limits. Despite these variations, all patients showed changes in the T waves. It is apparent that serum-potassium levels do not correlate with electrocardiographic changes in insulin-shock therapy. In this respect the findings are in accord with those reported by Tarail [6d] and with the observation that the concentration of serum potassium does not necessarily indicate the state of repletion or depletion of cellular potassium.[7] One of us (H. S.), in a previous study on potassium metabolism with relation to digitalis toxicity, pointed out that there was no consistent decrease in serum-potassium levels even when potassium loss was induced and digitalis sensitivity increased.[8] Unquestionably, the serum-potassium concentration of the blood does not reflect either the intracellular- or the extracellular-potassium state. This might explain, therefore, why the electrocardiographic changes appear in the face of such variations in serum-potassium levels. Furthermore, theoretically, hypoglycemic shock might affect the adrenal physiology of different patients in varying degrees, assuming that serum-potassium changes are mediated via the adrenal gland in shock states. Again, the serum-potassium concentration might be influenced by stimulation of the autonomic nervous system, as might occur during insulin-shock hypoglycemia. Potassium salts are also intimately related to the neurohumoral mechanisms and to the physiology of the autonomic nervous system.[9] Some investigators [9d, f] have reported that epinephrine or splanchnic-nerve stimulation liberates potassium from the liver. Other clinical investigators have demonstrated, too, that there are no consistent changes in serum-potassium concentration in insulin-shock therapy. They have pointed out that in some subjects the lowest serum-potassium levels are reached

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two hours before coma; in others, this occurs during coma, while in still others, instead of a fall, there is a rise in serum-potassium concentration.[10] If the correct time for drawing the sample from a particular patient is missed, it is possible that a much lower serum-potassium level may have been reached but gone undetected. This is of interest in light of the finding of focal cardiac lesions in animals in which a potassium deficiency had developed.[11] During undetected low serum-potassium levels such cardiac lesions or disturbances in cardiac physiology may have developed in our patients, and these would alter the electrocardiographic tracings.

This study does indicate that the oral administration of potassium salts simultaneously with the intramuscular injection of insulin will prevent the changes in T waves during the hypoglycemic shock period. Actually, the T waves increased in amplitude to values equal to or above those of the control tracing. At the same time, the serum-potassium concentration rose to high normal or above normal. Whether there is physiologic restitution of intracellular-potassium depletion can only be surmised.[8] It appears that potassium salts are as essential to normal cardiac physiology and histology as they are to brain-tissue metabolism.[12] Stark has pointed out the need for the administration of potassium in prolonged insulin shock.[13]

We have observed several patients whose onset of coma was delayed by the oral administration of potassium chloride. In addition, in this study, one patient failed to rouse from his coma after the administration of glucose, whereas when potassium chloride was given there was a prompt reaction.

SUMMARY AND CONCLUSIONS

Patients in hypoglycemic shock demonstrate electrocardiographic changes, such as a depressed T wave and sagging of the S-T segment.

Oral administration of potassium chloride simultaneously with the injection of insulin reverses these electrocardiographic abnormalities and raises the serum-potassium level.

There is no correlation between serum-potassium concentrations and changes in the electrocardiographic pattern. Some theoretical considerations have been offered to explain this discrepancy.

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INTRACRANIAL METASTASIS OF SARCOMA BOTRYOIDES

LESTER M. FRIEDLAND, M.D.
BROOKLYN

MIXED mesodermal neoplasms of the uterus, of which less than 100 cases have been reported, are often divided into two groups, cervical and corporeal, the former being commoner in children and young adults and the latter in women past the menopause. The descriptive term "sarcoma botryoides," first applied by Pfannenstiel in 1892, has been used since that time to include the gross grape-like appearance of the lesion in the uterus and the mixed microscopic features, which vary somewhat in the cases reported to date.[1] No instance of intracranial metastasis has been found previously recorded.

REPORT OF A CASE

C. G., a Negro woman aged 39, was first admitted from the outpatient department to the gynecology service of Kings County Hospital on June 7, 1945, because of an abdominal mass and a fungating, reddish mass attached to the cervix, with a clinical diagnosis of malignant neoplasm and/or fibroids. The polyp, uterus, tubes, and ovaries were removed. The uterus measured 18 by 12 by 10 cm. Approximately two-thirds of the endometrium was occupied with yellow and gray, spongy, grape-like structures, extending up from the endocervical lining. There were also multiple intramural, subserous, and submucous fibromyomas. The Fallopian tubes were somewhat thickened. Microscopic examination of the polyp showed myxomatous connective tissue (Fig. 1) and embryonal striated muscle, in which cross striations were easily demonstrable. The uterine neoplasm showed a similar architecture and also islands of cartilage.

The patient was readmitted on July 14, at which time another biopsy showed recurrence of myxomatous connective tissue, similar in architecture to portions of the neoplasm previously described. A course of x-ray therapy to the pelvis was given. On a third admission, on Nov. 5, polypoid tissue present in the cervix was cauterized and conized. A biopsy was again reported as showing recurrent botryoid sarcoma.

The patient's fourth admission, on Dec. 14, was to the fracture service because she had fallen while getting off a trolley car, struck her right leg, and sustained a fracture of the right femur. Roentgenograms showed irregular bone absorption in the femur and the frontal bones of the skull. On Jan. 18, 1946, a cystic swelling developed over the left eye, from which bloody fluid was aspirated. The possibility of abscess or epidural hematoma was entertained, and on Feb. 11 a left frontal craniotomy was performed, at which gelatinous tumor tissue, occupying the left anterior fossa, was encountered. Biopsy showed myxomatous connective tissue, similar to that found in previous specimens (Fig. 2), and was reported as metastatic sarcoma botryoides. After the operative procedure the patient's condition progressively declined, and she died on March 14, 1946.

From the Division of Neuropathology, Department of Pathology, Kings County Hospital.

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Autopsy.—Inspection revealed enlarged left supraclavicular and inguinal lymph nodes, an abdominal scar extending from the symphysis to the umbilicus, decubitus ulcers, fracture of the right femur, proptosis of the left eye, and multiple soft subcutaneous tumors extending into the left orbit. The lower third of the peritoneal cavity was filled with friable gray, glistening, moderately hemorrhagic tumor, resembling fish flesh; the ureters were embedded in tumor and

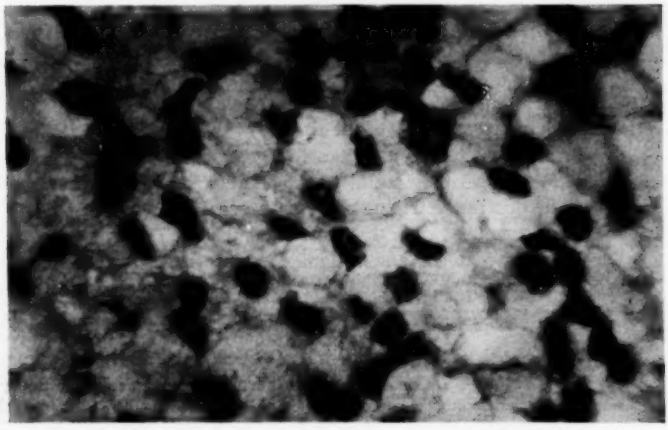

Fig. 1.—Myxomatous connective tissue in the primary tumor; × 430.

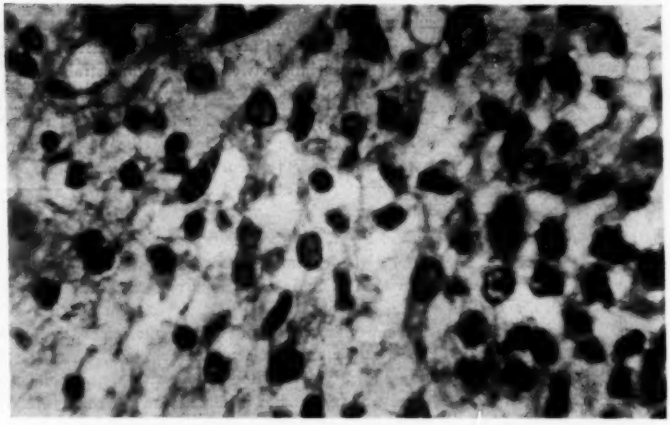

Fig. 2.—Myxomatous connective tissue in the intracranial metastasis; × 430.

bilaterally dilated above. There were multiple pulmonary and pleural metastases. Portions of the serosa of the large bowel and lower portion of the ileum were involved by tumor. There was red friable tumor in and around the fracture site in the right femur.

In the cranial cavity, a tumor mass was present in the left temporal region, measuring 3.5 by 3 cm. There was 10 cc. of blood beneath the dura. In the left frontoparietal region and the left orbit there were large, confluent masses of tumor tissue. The brain weighed 1,200 gm. The orbital surface of the left frontal lobe was deficient and was indented up to the left precentral

gyrus by a soft gray, brown, and orange, friable, gelatinous neoplasm. There was deviation of the left olfactory region and uncus medially and caudally, compressing the left third nerve. Microscopic examination of the intracranial neoplasm showed chiefly myxomatous connective tissue, similar to portions of the neoplasm elsewhere. Sections stained by the Foot-Goldner modification of the Masson trichrome stain distinguished the cells from astrocytes, which they superficially resembled.

HISTOLOGY

The components of botryoid sarcoma are, most frequently, mesenchymal or myxomatous tissue, cartilage, and striated muscle. Other tissues, identified by previous observers, include epithelium, "giant cells," smooth muscle, bone or osteoid tissue, fat, endothelium, and nerve tissue, in decreasing order of frequency. The simultaneous presence of striated muscle and cartilage is uncommon, having been observed in only 4% of cases.

HISTOGENESIS

The origin of mixed mesodermal neoplasm of the uterus is speculative, the chief theories being the two familiar ones of metaplasia with neoplastic formation and origin from embryonal rests or heterotopic tissue. Associated fibroids are present in about 8% of cases. Such a low incidence would seem to exclude, at least statistically, origin from this group of benign neoplasms. Some observers have described cartilage, bone, and even striated muscle, in rare instances, in an otherwise normal uterus at autopsy. The "nervous tissue" reported in two instances, if truly neoplastic, would be difficult to account for in a mesodermal tumor unless the much-disputed integrity of the germ layers were again impeached.

CLINICAL COURSE

The general mortality rate is 90% despite surgical and x-ray therapy, the average duration of life being about one year. Death is usually due to hydronephrosis from ureteral obstruction or to cachexia from metastases.

SUMMARY AND CONCLUSIONS

A case of sarcoma botryoides of the uterus in a Negro woman aged 39, with complete autopsy, is reported. The neoplasm contained both striated muscle and cartilage, in addition to mesenchymal connective tissue, was associated with fibroids, and metastasized to the cranial cavity.

UNILATERAL AND BILATERAL LOBOTOMY

A Controlled Evaluation

ALEXANDER SIMON, M.D.
LESTER H. MARGOLIS, M.D.
JOHN E. ADAMS, M.D.
AND
KARL M. BOWMAN, M.D.
SAN FRANCISCO

THE GROWTH of psychosurgery as an adjunct in the treatment of mental illness is reflected in the increasing number of operations on the frontal lobe performed in the past 15 years. Although the method was not introduced until 1936, by March, 1947, over 2,000 lobotomies had been done in the United States, 1,725 of this number since 1941.[1] By June, 1948, the number had grown to approximately 5,000[2] and by October, 1949, to over 10,000.[3] Despite this rapid growth, there exists considerable controversy as to many aspects of the operation. Studies to date leave unclear the relative efficacy of various modifications in surgical approach, the optimum plane of section, the site of ablation, and the quantity of cortex to be isolated. The extent, duration, and specificity of emotional, intellectual, and personality defects require further elucidation. Moreover, there is need to evaluate the therapeutic effects of the psychic trauma involved in such an operation.

The work of Meyer and Beck[4] illustrates the nonspecificity of "cures" or "improvements" in certain seemingly therapeutically hopeless patients in whom almost no evidence of surgical damage to the frontothalamic connections was seen at autopsy. Guttman,[5] in his observations on depressive patients who recovered

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Presented at the annual meeting of the California Medical Association on May 14, 1951, at Los Angeles.

From the Divisions of Psychiatry and Neurosurgery, University of California School of Medicine, San Francisco, and The Langley Porter Clinic, Department of Mental Hygiene, State of California.

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after self-inflicted brain injuries, concluded that recovery in certain cases was due not to the frontal-lobe injury, but to the combined operation of physical and psychologic factors. The general damage to the brain and the effect of the injury upon the patient, along with the release of tension in the suicidal act, the integration of the illness as a physical rather than a mental one, the amnesia, and the resultant alteration in the life situation all play a part in producing the "recovery."

Although workers from widely different sources have reported strikingly uniform results and personality defects after operation, these observations do not serve to explain the nonspecific cures which have been cited. It has also been pointed out by many that schizophrenia, the illness most frequently treated by psychosurgery, has been observed to respond favorably to such a variety of procedures and circumstances as to indicate an almost certain psychologic influence. Another difficulty attending the interpretation of results of lobotomy has been the great variation in the types, severity, and duration of the psychoses selected for operation. Although a clearer formulation of the criteria for operation has gradually been made, this has not entirely excluded numerous early cases which may have displayed spontaneous improvement without an operation.

Such controversy serves to highlight the need for control studies in evaluating lobotomy projects. At least one study has been carried out in which groups of patients with operation and of patients without operation were matched for all possible factors. The difficulties attending this have been well documented in the report of the Columbia-Greystone Associates.[1]

> It is evident that very strenuous efforts must be used and a hospital population larger than 6,000 to obtain 48 psychiatric patients who are relatively uniform with regard to more than one or two variable factors.

It has also been suggested[2] that an ideal control group would be one "falsely" lobotomized by having burr holes made and the dura cut, information as to the surgical differences between the two groups being available only to the neurosurgical team. Even if one could obtain a so-called control group of patients with pseudo lobotomies who were matched as to such factors as age, race, intelligence, education, social and economic status, symptoms, duration of illness, duration of hospitalization, duration and type of previous therapy, and premorbid personality, there would still remain so many other variables which could not be matched that a scientifically adequate control group would be impossible to find. Such an experiment would also be subject to criticism in that the staff responsible for the patients' care would quickly distinguish controls from the patients lobotomized and would accord them different treatment and attitudes. In general, the individual patient and his adjustment and course prior to operation can be considered the best control for his condition after operation.

Having in mind these factors, it was our purpose in this study to assess the effects of frontal lobotomy by utilizing as far as possible a control series for comparison. Since our physical resources and patient material would not permit either an adequate "matching" of patients or the according of identical "convalescent" treatment to controls and lobotomized patients, it was necessary to seek another method. It was thought that our purpose could be best achieved by doing by chance selection equal numbers of unilateral and bilateral lobotomies under conditions

which would keep the extent of the operation unknown to all except the neurosurgical team for a period of six months. If the effects of the operation are due to the relative completeness of the operation or the amount of frontothalamic connections severed rather than to less tangible factors, such as the psychologic influence of the procedure, there should be an appreciable difference in the results in these two groups. However, a comparison of the effects in these two groups might be vitiated by the possibility that the staff could detect behavioral differences and distinguish which patients had unilateral and which had bilateral lobotomies, or by the possibility that chance selection might throw more hopeful prospects into one group or into the other. These objections could be offset by using the group with unilateral lobotomy as its own control by subjecting it to a contralateral operation after approximately six months of convalescence if little or no improvement had occurred. It is generally considered that a unilateral lobotomy offers little therapeutic prospect for improvement in mentally ill people, especially patients with chronic schizophrenia, such as those treated in this study.[3] Such a procedure would also permit a study of the effects of unilateral lobotomy in psychotic patients.

PROCEDURE

Case Material.—Patients were selected by the staffs of nearby state hospitals. All were chronically ill, for whom all available types of therapy, including electroconvulsive and/or insulin coma therapy, had failed; all presented severe management problems and were judged to have a poor or hopeless prognosis without surgical intervention. No patient was accepted because of the insistence of the family that an operation be done. However, the consent of the family, its interest in the patient, and its potential ability to assist in the patient's rehabilitation were considered. The patients were selected by the staffs of these hospitals on an extremely conservative basis, with as much or more emphasis on alleviation of management problems as on selection of good therapeutic prospects. This, in part, is evidenced by the average duration of illness of 8.8 yr. for the 33 patients described in this study (Tables 1 and 2).

Preoperative Studies.—After being selected as candidates for lobotomy, the patients were transferred to The Langley Porter Clinic, where the following preoperative studies were carried out: A complete history was obtained from all available sources (state hospital chart, family and patient). Physical, neurologic, and psychiatric examinations were done. Complete blood counts; urinalyses; blood serological tests; blood typing, roentgenographic studies of the chest, skull, and spine; electroencephalographic tests, and psychological tests were carried out. Patients who were mute, unresponsive, or out of contact were often tested during a "sodium-amytal® interview." Pneumoencephalograms were obtained in selected cases. Electroconvulsive therapy was frequently necessary during the preoperative observation period for its sedative effect on the more agitated and disturbed patients.

In most instances there was agreement between our staff and the referring staff as to suitability of patients for operation. Disagreement occurred when the patient was sent in relatively good contact after having received intensive electroconvulsive therapy prior to his transfer. Such doubts on our part were generally dissipated when, within a few days or weeks, the therapeutic effects of previously administered electroconvulsive treatment diminished and the psychotic manifestations became more overt. When, for one reason or another, our staff did not concur in the recommendation for lobotomy, as occurred in four instances, and the patient was returned to the referring source without an operation, or kept in The Langley Porter Clinic for intensive psychotherapy or further somatic therapy, subsequent events proved that we were unnecessarily conservative. Another factor entering into selection of operative candidates was the conservatism of the neurosurgeons. Patients who were over 60 years of age, or who showed advanced arteriosclerosis, or who had questionably active pulmonary disease, or who were cardiac risks were not selected for the operation.

It was originally intended to have equal numbers of men and women in the series, but several factors operated to produce a preponderance of females. The physical and personnel resources of the hospital did not permit the handling of severely disturbed, aggressive, assaultive, or combative patients who would require isolation or restraint and who could not be managed with the aid of electroconvulsive therapy. Nor were facilities available for complete separation of the sexes. Since the majority of referrals were women, and since we were at a disadvantage in attempting to keep only a few male patients in an otherwise all-female ward, it soon evolved that we were accepting almost entirely women (30 of 33).

The period of preoperative study was usually about three to four weeks, but occasionally the operation was delayed for as long as two months while previously unrecognized systemic diseases were being studied or treated. After operation the patients were kept for another period of two to four weeks, or longer if complications ensued. Most patients were transferred back to their referring hospital, but a few displayed sufficient improvement to be tried on short visits home and then placed on extended leave in the care of their families.

Patients were operated upon for the most part in the order of their admission to the hospital. A code key was drawn up by an indifferent staff member and kept in the neurosurgeon's possession. This key determined whether any given patient was to have a unilateral or bilateral operation, insuring a chance selection as to the extent of the operation. Identical scalp incisions were made for both the unilateral and the bilateral operations. If a unilateral operation was to be done, the surgeon was free to choose whether this should involve the right or the left side. The ward personnel was not informed as to the nature of the operation, and the operative note was not incorporated in the chart. Since the postoperative electroencephalogram might point to a lesion in one or both frontal lobes, these reports also were not made available to the staff. It developed that the ward staff was able to guess correctly which patients had bilateral and which had unilateral lobotomies. However, the patient's postoperative stay at The Langley Porter Clinic was limited to only a few weeks, and these deductions were not available to the state hospital staffs responsible for the major part of the patient's convalescent care.

Surgical Technique.—All operations were performed by the neurosurgical staff of the University of California Hospital. An identical scalp incision was used for both a unilateral and a bilateral operation, the incision being 10 cm. in length and placed parallel, and just anterior, to the coronal suture line. The trephine openings (or opening in the case of a unilateral operation) were made just at the coronal suture line, approximately 3 cm. lateral to the midline. After the dura was opened and retracted and a portion of cortex removed for pathologic study, the plane of section was established by inserting a ventricular needle to the base at the posterior border of the sphenoidal ridge. The section of white matter was then carried out under direct visualization by means of a narrow ribbon retractor, using a combined bovie-suction unit. If the ventricle was encountered and it was necessary to enter and pass through the tip of the ventricle in order to obtain an adequate section, this was done. After the section had been completed, the sphenoidal ridge was again identified by the ventricular needle as a check on the accuracy of the plane of section. Hemostasis was established by means of cautery and irrigation.

CLINICAL OBSERVATIONS

Reliability of Conjecture as to Extent of Operation.—Our surmises as to the type of operation were based upon the early postoperative behavioral differences in the two groups of patients. Of the 16 patients who were thought (and subsequently found) to have had[6] bilateral lobotomy, 14 showed increased apathy and "emotional flattening"; 12 were incontinent; 11 were generally unaware of having had an operation, and only 1 complained of headache. None of the group

6. These guesses were not checked for correctness until after the patient had been seen six months after operation and a second series of opinions ventured, after which the staff was informed for the first time of the exact extent of operative intervention.

with unilateral lobotomy exhibited a significant increase in apathy; only 3 of the 17 were incontinent; only 5 were unaware of having had an operation, and 9 complained of headache.

In certain cases clear-cut postoperative behavioral changes were masked by the preoperative incontinence, mutism, extreme apathy, and withdrawal, which in many instances could not be reversed even with the patient under amobarbital (amytal*) narcosis. In spite of this, correct guesses as to the type of operation based on the first two to three weeks of postoperative behavior were made by all observers in 31 of the 33 cases. In two instances, in which the patients had a bilateral lobotomy and showed few of the expected postoperative changes, incorrect guesses were made.

When these patients were seen again by five or six members of The Langley Porter staff, approximately six months after operation, reports on their clinical course were presented by the state hospital staff, and they were interviewed in a staff-group setting. At this time correct guesses were made by all observers in 28 of the 33 cases and by almost all observers in 30 of the 33 cases. In two instances one of six observers erred in thinking that the patient had had an inadequate bilateral operation, whereas the other five examiners guessed correctly that a unilateral operation had been done. The two patients whose type of operation had originally been wrongly guessed six months previously were again thought to have had a unilateral, rather than a bilateral, lobotomy. It is possible that these two patients received inadequate sections and that they would respond to a revision of the original lobotomy. Another patient was not seen at this time but was brought to us by her husband, who felt that she was adjusting poorly while on leave. She was seen by two of us (A. S. and L. H. M.), and, without benefit of the state hospital observations, both of us were wrong in guessing that she had a unilateral, rather than a bilateral, section.

Clinical Course.—In most of the patients whose condition was changed as a result of the operation, the improvement was manifested rather early and was progressive. However, in one patient with bilateral lobotomy there was an abrupt initial change, but a complete relapse in a few months. This condition remained stationary for a year, after which a second operation resulted in marked and sustained improvement. Another patient, although slightly improved after a bilateral operation, remained mute and catatonic for the most part for four months, at which time she made a sudden and dramatic improvement and was able to adjust at home. There was no obvious psychologic or environmental factor to explain this sudden change. One of the patients in the group with bilateral lobotomy relapsed slightly between the 6- and the 12-month evaluation, but the rest maintained their condition over this interval.

Complications.—Surgical complications in these patients were few. In one of the group with bilateral lobotomy necrosis of the right frontal lobe developed, presumably owing to damage to the right anterior cerebral artery. This necessitated excision of the involved lobe, after which the postoperative course was essentially similar to that of the other patients in this group. A patient who was slightly improved six months after a unilateral lobotomy had intracranial bleeding after the contralateral operation. The hematoma was successfully evacuated, but the patient

was left with aphasia and hemiplegia. There were no deaths in this series, but in a total of 136 lobotomies performed at this clinic with the technique described in the text there were two deaths.

During the first six months after operation, convulsions developed as a complication in two patients with unilateral lobotomy and in three patients with bilateral lobotomy, and subsequently in another patient in each group. In a patient who was having convulsions prior to operation the frequency of the convulsions was unchanged after a unilateral operation and, again, six months after a contralateral operation. In all these patients the seizures were well controlled when an anticonvulsant regimen was instituted. It is possible that the high incidence of convulsions in this series has been due to the fact that in each case a rather large biopsy specimen of cortex was taken for neuropathologic and metabolic studies.

TABLE 1.—*Clinical Data on Fifteen Patients with Chronic Schizophrenia and One with Paranoid Involutional Psychosis Subjected to Bilateral Lobotomy*

Patient	Age, Yr.	Duration of Illness, Yr.	Result*		Benefited by Operation		Convulsions	Comment
			6 Mo.	12 Mo.	6 Mo.	1 Yr.		
1	55	22	+	+	Yes	Yes	....	.....
2	34	11	+	+	Yes	Yes	....	.....
3	61	8	++	++	Yes	Yes	....	.....
4	35	10	+	+	Yes	Yes	Yes	Right frontal necrosis and lobectomy
5	38	9	+	+	No	No	....	.....
6	31	4	+	+	No	No	....	.....
7	23	3	+++	+++	Yes	Yes	Yes	Excellent home adjustment
8	27	5	+	+	No	No	....	.....
9	34	14	+	+	Yes	Yes	....	.....
10	28	4	+	+	Yes	No	....	Slight relapse after 6 mo.
11	25	3	++	++	Yes	Yes	Yes	.....
12	31	4	+++	+++	Yes	Yes	Yes	Sudden improvement after 4 mo.; good home adjustment
13	42	3	++	++	Yes	Yes	....	.....
14	41	11	+++	+++	Yes	Yes	....	Fair adjustment as housewife
15	27	3	+	+	No	No	....	.....
16	33	16	—	—	No	No	....	Home; much improvement after more radical operation

* The minus sign (—) indicates no improvement; +, slight improvement; ++, moderate improvement, and +++, much improvement.

Criteria for Therapeutic Evaluation.—The results of lobotomy were evaluated according to the following criteria:

1. Condition much improved (+++). The patient displays no overt symptoms except for evidence of slight emotional dulness or anxiety, is well enough to function acceptably in a social milieu outside the hospital, is able to work for a living or as a housewife, and is often described by the family as "recovered" or "as good as ever."

2. Condition moderately improved (++). The patient displays a definite reduction in quantity and intensity of psychotic behavior and symptoms, which, however, are still apparent; he makes a better ward adjustment (occupationally and socially), is cooperative and coherent in speech, and no longer needs electroconvulsive therapy to control disturbed behavior. Such a patient may adjust at home in a well-supervised, accepting family situation.

3. Condition slightly improved (+). The patient exhibits only slight reduction in quantity and intensity of psychotic behavior and symptoms; he may display disturbed and assaultive behavior on occasion, may need urging to communicate, to feed himself, or to work and may continue to be incoherent and irrelevant in speech.

In a number of this group, the over-all degree of improvement may be dramatic as compared with the preoperative behavior. The patient has become a much easier nursing problem even if the underlying schizophrenic process remains essentially unchanged. In Tables 1 and 2, this portion of the "slightly improved" (+) group is listed with the "moderately improved" (++) and the "much improved"

TABLE 2.—*Clinical Data on Sixteen Patients with Chronic Schizophrenia and One with Involutional Psychosis, Paranoid Type, Subjected to Unilateral Lobotomy, Followed in Fourteen Patients by Contralateral Lobotomy*

Patient	Age	Duration of Illness, Yr.	Side of Operation	Result*	Benefit	Interval, Mo.	Reoperation†	Result 6 Mo.*	Benefit	Convulsions	Comment
17	39	10	R	+	No	7	L+	+	Yes	....	.....
18	37	6	R	+	No	6	L	—	No	Yes	.....
19	38	18	L	+	Yes	6	R+	++	Yes	....	.....
20	33	4	R	—	No	5	L	+++	Yes	....	.....
21	27	6	R	—	No	5	L	+++	Yes	....	Home on isolated ranch since last operation
22	27	3	L	—	No	6	R	—	No	Unchanged	Convulsive state unchanged by operations
23	38	6	L	—	No	6	R+	+++	Yes	....	.....
24	36	5	L	—	No	6	R+	++	Yes	....	.....
25	50	11	L	+	No	6	R+	++	Yes	....	.....
26	38	18	L	+	No	3	R+	++	Yes	Yes	.....
27	42	22	R	+	Yes	8	L	++	Yes	....	.....
28	36	10	R	—	No	6	L	+	Yes	....	.....
29	28	2	L	+	No	6	R+	+	Yes	....	.....
30	55	14	R	+	No	6	L	—	No	Yes	Hemiplegic and aphasic since 2d operation
31	26	8	R	—	No	12+	..	....	....	....	.....
32	20	8	L	—	No	12+	..	....	....	Yes	Home on isolated ranch since operation
33	43	11	R	+++	Yes	12+	..	....	....	....	Excellent adjustment as housewife

* The minus sign (—) indicates no improvement; +, slight improvement; ++, moderate improvement, and +++, much improvement.

† L+ (or R+) indicates the contralateral operative section plus revision of the original side.

(+++) group as "benefited" by the operation, whereas those in the "slightly improved" group showing a less dramatic change are listed with the "unimproved" group as "not benefited."

The course of Patient 27 serves to illustrate such limited, but gratifying, improvement. This woman, after 22 years of illness and 17 years of hospitalization presented the picture of chronic "deterioration," and her sole activities, aside from occasional assaultive outbursts, consisted of sucking her thumb, drooling, and muttering unintelligibly to herself. After unilateral lobotomy, she was able to participate in ward activities, could speak relevantly for short periods, wrote letters to her family, exhibited much less pronounced mannerisms. She was then described as "slightly improved." After a contralateral lobotomy, her verbal pro-

ductions were still silly and rambling, but she was in much better contact, made herself a ward favorite by her teasing, provocative behavior, was able to go out on leaves with her family, and on one such occasion displayed enough initiative to sneak away from the family and go downtown, where she was found "shopping" several hours later. She was classified as "moderately improved" at this time.

4. Condition unimproved (—). The mental state is essentially unchanged.

Results.—Only after it was revealed which patients had received bilateral and which unilateral operations were the results in the two groups compared. Of the 16 patients with bilateral lobotomy, at the six- and 12-mo. postoperative periods, three were considered much improved and adjusting well at home. Three were moderately improved; nine were slightly improved, and 1 was unimproved (Table 1). Eleven were considered benefited as a result of the operation. Of the 17 patients with unilateral sections, six months after operation, one was much improved and making a good adjustment at home; none was moderately improved; eight were slightly improved, and eight were unimproved (Table 2). Two of the last group, although unimproved, were able to continue the marginal adjustment they had made on their parents' isolated ranch prior to their operation. Only three were considered benefited as a result of the operation. In 10 of these patients the right side was sectioned, and in seven the operation was performed on the left side, and the results were essentially the same in the two groups.

Fifteen of the patients in the group subjected to a bilateral operation had schizophrenia, and one, an involutional psychosis, paranoid type. The age range was from 23 to 61, with an average of 35.6 years. The duration of illness varied from three to 22 years, with an average of 8.1 years. Sixteen of the patients in the group with unilateral lobotomy were schizophrenic, and one had involutional psychosis, paranoid type. They ranged in age from 20 to 55, with an average age of 36. The duration of illness in this group varied from two to 22 years, with an average of 9.5 years.

No dogmatic conclusions can be drawn from such a small series, but it is readily apparent that there were marked differences in postoperative behavior and clinical results in the two groups. Electroencephalographic and psychologic studies revealed significant differences between them, but the details will be reported in further communications. After six months of observation, it appeared that significant improvement (including much improvement and moderate improvement and the slight improvement in patients whose change for the better, although slight, was gratifying to those caring for them) had occurred in 11 of 16 patients (68.8%) subjected to bilateral lobotomy but in only three of 17 patients (17.6%) undergoing a unilateral operation (Tables 1 and 2). In another series of patients unilateral lobotomies were performed on a selective basis, but these will be reported in another communication.

The response of Patient 33 to unilateral lobotomy merits special mention because it represents a striking exception to that of the other patients with unilateral lobotomy. The patient, a woman aged 43, had been ill for 11 years and hospitalized almost continuously for five years. Her illness was diagnosed under "schizophrenia, other types, with paranoid and affective features," and was characterized by delusions that eating was a sin, and was like putting "garbage" into the body, that her food was being poisoned and her relatives were against her, that she had committed

many sins, and that she had been changed as a result of "magic" influences. These ideas were conveyed to her in auditory hallucinations. She was seclusive, agitated, and depressed and required tube feeding. She received 70 electroconvulsive treatments over a two-year period, without significant lasting benefit, and was then referred for lobotomy.

Lobotomy was done on the right side, after which improvement was immediate in that she no longer was a feeding problem, was able to participate in ward activities, socialized and jested with other patients and members of the ward staff, and no longer expressed delusional ideas. She was permitted to go home 16 days after operation, and adjustment was so good that this "visit" has continued for 14 months. She now does all the housework, shopping, laundry, cooking, and cleaning for her family and attends interior-decorating and cooking classes in her spare time. She claims complete amnesia for her illness and appears cheerful and alert. The only questionable aspect of her adjustment is her feeling that her mood is influenced by colors and her refusal to ride elevators. The family feels that she is completely well.

Effect of Contralateral Operation on Patients with Unilateral Lobotomy.—In order further to validate the hypothesis that the effects of the operation were dependent on its extent more than on the less tangible psychologic factors, it remained to show whether a contralateral lobotomy would effect further changes in the group which displayed little or no improvement from a unilateral operation.

Accordingly, after the six-month [7] evaluation was made, 14 of the 17 patients who had had unilateral lobotomies were returned to The Langley Porter Clinic, where the preliminary studies were repeated and lobotomy was performed on the contralateral side and, in seven instances, the initial section also revised. In each of these seven cases in which the site of the initial lobotomy was reexplored, the section was found to be relatively complete, and it was felt by the neurosurgeon that little was gained by reoperating in a plane slightly posterior to the residual gliosis. At the time of this report two of the 17 patients have not had a second operation because the family would not consent to one. Another was so greatly improved by the unilateral lobotomy that a second operation was not felt to be indicated. Of the 14 patients thus reoperated on, a six-month follow-up study revealed great improvement in three, moderate improvement in five, slight improvement in three, no change in two, and a worsened condition, owing to postoperative complications, in one. Whereas a unilateral operation in this group had proved beneficial in only three of 17 (17.6%) patients (and in 2 of the 14 patients [14.3%] who were reoperated on), when 14 of the same patients underwent lobotomy on the contralateral side beneficial results were achieved in 11 (78.6%). The results of a unilateral and a second, contralateral operation in each of these patients are compared in Table 2.

SUMMARY

In order that the importance of the psychologic influence of operative intervention in the therapeutic efficacy of frontal lobotomy might be evaluated, 33 chronically psychotic patients were studied. These patients received either a unilateral or a

7. This is an approximate figure. The time interval between the first and the second operation was three months in one case and varied from five to eight months in the remainder.

bilateral lobotomy by chance selection under conditions in which the extent of the operation was unknown to the personnel responsible for the patients' postoperative care.

Of the 16 patients with bilateral operations, beneficial results were obtained in 11 (68.8%) six months after operation.

Of the 17 patients with unilateral operations, beneficial results were obtained in only three (17.6%) six months after operation.

Fourteen of the patients with unilateral operation were subjected to a second-stage, contralateral operation. Six months later beneficial results were observed in 11 of them (78.6%).

It is concluded that (*a*) the psychic trauma of operative intervention is not an important factor in determining the therapeutic benefits derived from a frontal lobotomy, and (*b*) except in rare instances, bilateral operation is necessary for beneficial results in the patient with chronic schizophrenia.

THE ELECTROENCEPHALOGRAM IN MULTIPLE SCLEROSIS

Analysis of a Series Submitted to Continuous Examinations and Discussion

VICTOR FUGLSANG-FREDERIKSEN, M.D.
AND
PAUL THYGESEN, M.D.
ODENSE, DENMARK

RELATIVELY few, and no continuous, electroencephalographic studies appear to have been made of patients with multiple sclerosis.

The object of the present work is to investigate and discuss to what extent the electroencephalogram reflects the activity, duration, localization, and gravity of the disease.

MATERIAL AND METHOD

The material comprises 74 inpatients and outpatients and is probably fairly representative of the disease. Forty-four patients were females and 30 were males. Eleven, or 15%, were less than 30 yr. of age, 2 being under 20 yr.; 37, or 50%, were 31 to 40 yr. of age, and 26, or 35%, were more than 40.

Fourteen, or 19%, had been ill less than two years; 17, or 23%, from two to five years; 20, or 27%, from five to 10 yr., and 23, or 31%, more than 10 yr.

The general gravity of the symptoms, expressed roughly in terms of occupational capacity, (corrected by means of ability tests for differences in the kind of occupation) are tabulated as follows:

	No.	%
Fully or partly able to carry on original occupation	20	27
Disabled in original occupation; capable of lighter work	22	30
Totally incapacitated, including 12 patients partly bedridden	29	39
Classification doubtful	3	4

Continuous electroencephalographic observation was practicable in only 64 cases, in which the electroencephalographic observation period averaged 8½ mo. (less than 6 mo., 18 cases; from 6 to 12 mo., 29 cases; from 12 to 18 mo., 17 cases). A total of 203 electroencephalograms were obtained, i. e., one record at an average interval of two and one-half months.

The electroencephalograms were interpreted without a knowledge of the clinical status, which was controlled by means of continuous clinical neurological examinations at intervals of less than one month.

The results of analysis of the clinical course will be reported in detail by one of us (P. T.), whereas the results of a simultaneous otoneurological control will be reported separately by Bentzen, Jelnes, and Thygesen.

Technique.—The electroencephalograms were recorded with a six-channel Kaiser electroencephalograph, which is in commonest use in Scandinavia. Sixteen electrodes were distributed over four longitudinal and four transverse leads. Both "monopolar" and "bipolar" recording were used. The patients were subjected to a two-minute period of hyperventilation.

In order to avoid too small groups, we classified the electroencephalographic findings of diffuse nature only as (1) normal electroencephalographic patterns, (2) slight general dys-

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From the Department of Neurology, Odense County and City Hospital, Denmark; Chief, Mogens Lund, M.D.

rhythmia, and (3) moderate to severe general dysrhythmia. In this classification we used the ordinary criteria, described, among others, by Gibbs, Gibbs and Lennox,[1] and by Jasper and Kershman.[2]

With regard to focal changes, most importance was attached to local preponderance of dysrhythmia and to phase reversals. The significance of these phase reversals has been stressed by Buchthal and Busch,[3] Hertz,[4] and others, and they were observed, for example, by Kershman and associates[5] in 50% of a series of cases of brain tumors.

Phase reversals were accepted only if they proved constant after the electrode placement had been changed. As the examinations were made on ambulatory patients, only a few patients could be subjected to repeated examination a few days later as a control of the actuality of the phase reversals, as suggested by Buchthal and Busch.[3]

RESULTS

The degree and nature of the electroencephalographic changes varied within wide limits. The commonest changes, in order of frequency, were as follows: slow waves of various frequencies (usually slightly or moderately reduced frequency); alternating, irregular rhythm; abnormal single potentials of various kinds (in no case, however, were there wave-and-spike patterns); high-voltage activity or normal frequency; base-line sway. Moreover, virtually every type of electro-

TABLE 1.—*Disease Activity During the Electroencephalographic Observation Period*

	No.	%
No or minor changes in symptoms (unchanged ability) *	20	31
One definite outburst †	18	28
Several definite outbursts †	16	25
Classification doubtful	10	16
Total	64	

* Not meaning inactive disease. Several patients of this group presented fluctuating sensory disturbances, subjectively altered visual impairment, slight disturbances of speech, or a temporarily increased feeling of paralysis. With this group are included the patients with possible dissemination of lesions to clinically "silent zones" in the central nervous system.

† Including only patients who presented prominent and objective signs of dissemination of lesions or recurrence of previous symptoms with increased severity.

encephalographic abnormality occurred in this series. Low-voltage rapid activity occurring as an isolated phenomenon was not interpreted as abnormal. The varieties of focal changes were also met with, but most importance is attached to phase reversals, which, despite their frequently inconspicuous character, appear to be of a certain clinical significance, to which we shall return later.

Clinical Neurological Observation.—The results so far as they concern the electroencephalographic findings will be reported in brief.

No conclusion can be drawn from these figures except that the patients with disease of the longest standing showed slight activity.

1. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Electroencephalographic Classification of Epileptic Patients and Control Subjects, Arch. Neurol. & Psychiat. **50:** 111 (Aug.) 1943.

2. Jasper, H., and Kershman, J.: Electroencephalographic Classification of the Epilepsies, Arch. Neurol. & Psychiat. **45:**903 (June) 1941.

3. Buchthal, F., and Busch, E.: Localization of Intracranial Tumors by Electroencephalography, Acta psychiat. et neurol. **22:**9, 1947.

4. Hertz, H.: Electroencephalografiens stilling i den neurologiske klinik, Ugesk. læger **112:**250, 1950.

5. Kershman, J.; Conde, A., and Gibson, W. C.: Electroencephalography in Differential Diagnosis of Supratentorial Tumors, Arch. Neurol. & Psychiat. **62:**255 (Sept.) 1949.

Further comparison goes to show that full working capacity decreases fairly evenly with increasing duration (from 43%, in cases of less than two-years' standing, to 13%, in cases of more than 10-yr. standing) without a corresponding increase in total helplessness (from 14 to 22%).

The incidence of symptoms will not be reported in detail, but the incidence of the symptoms with which we are concerned in the present paper will be seen from a later tabular comparison with the electroencephalographic findings.

TABLE 2.—*Relation of Disease Activity to Duration of Disease*

	Total	Duration of Disease (Yr.)			
		<2	2-5	5-10	>10
No or minor activity	20	3	5	4	8
One outburst	18	2	6	5	5
Several outbursts	16	3	5	7	1
Doubtful activity	10	2	1	3	4
Total	64	10	17	19	18

TABLE 3.—*Summary of Results in 203 Electroencephalographic Recordings*

	Total (74)	Patients Reexamined (64)
Normal EEG on all occasions	18 (24%)	12 (19%)
Abnormal EEG on one or more recordings	56 (76%)	52 (81%)
Nature and localization of abnormalities		
No general dysrhythmia	32	24
Slight general dysrhythmia	34 (57%)	32 (63%)
Moderate to severe general dysrhythmia	8	8
Difference in dysrhythmias of the two hemispheres	13	13
Occipital preponderance of dysrhythmia	16	14
No phase reversals	42	34
Phase reversals	32 (43%)	30 (47%)
Exclusively unilateral	24	23
Exclusively bilateral	5	4
Unilateral, as well as bilateral	3	3
Occipital localization	29	27
Onset and course of abnormalities	Dysrhythmia	Phase Reversals
Manifest prior to, persisted throughout observation period	25	2
Manifest prior to, remitted during observation period	4	10
Manifest during, persisted throughout observation period	9	5
Manifest during, remitted during observation period	2	13
(Recurrence after a remission)	(1)	(4)
Degree of dysrhythmia changed during observation period	29 (45%)	
Increasing	15	
Decreasing	7	
Fluctuating	7	

About half the patients presented one or more "brain-stem symptoms," in this paper including diplopia and/or objective ophthalmoplegia externa, trigeminal symptoms, and facial weakness of predominantly peripheral or nuclear type.

The onset of these symptoms is usually comparatively acute; they occur oftener in combined than in isolated form, and, except for facial paralysis, they have often shown remission before the expiration of the observation period. The attendant symptoms referable to the extremities are characterized by incoordination rather than by paresis and spasticity.

About half the patients had spontaneous nystagmus, accompanied in about 50% by pathologically prolonged reaction on vestibular stimulation (caloric, rotatory, or amyl nitrite test). About 20% revealed abnormal hearing in tuning-fork and

tone-audiometer experiments. Several exhibited discriminative difficulties in the speech tests (despite a normal perception of tones). The acoustic and vestibular abnormalities were also chiefly transitory.

Spontaneous fixation nystagmus and pathological induced nystagmus appear to be due predominantly to lesions of the brain stem, unlike spontaneous nystagmus of the position or end-position variety.

Electroencephalographic Observation.—The results are presented in Table 3.

Abnormal electroencephalograms were obtained at one or more recordings in three-fourths to four-fifths of the cases (depending on the length of the observation period). In three-fourths (42 of 56) the abnormalities included general dysrhythmia; in about three-fifths (32 of 56), phase reversals.

In the majority of cases, the dysrhythmia was slight or moderate and of a diffuse nature, combined with a certain amount of focal signs. The phase reversals were usually unilateral. We shall return to their significance, as well as the significance of the occipital preponderance of the abnormalities observed in a number of cases. The phase reversals appeared to be particularly transitory, whereas the dysrhythmia was somewhat more stable; nevertheless, the intensity of the latter changed in the course of the observation period in no less than three-fourths (29 of 40) of the cases.

The longer the observation period, the larger the number of abnormal findings, as shown in the following tabulation:

	Duration of Observation Period, Mo.		
	Less Than 6	6-12	12-18
New abnormalities became manifest in	17%	45%	59%

Relation of Clinical to Electroencephalographic Findings.—Age and the general gravity of symptoms, in terms of ability, did not influence the number (and distribution) of electroencephalographic abnormalities.

	Normal EEG, %
Age	
<30	18
31-40	24
>40	21
Ability	
Fully or partly capable of working	24
Incapacitated (possibly bedridden)	24

There is an apparent relation between the duration of the disease and the electroencephalographic findings, as shown in Table 4.

TABLE 4.—*Duration of Disease in Relation to the Electroencephalographic Pattern*

Duration of Disease, Yr.	Total	Normal EEG	General Dysrhythmia	Altered Dysrhythmia	Phase Reversals
<2	14 (10)*	3	8	(4)*	6
2-5	17 (17)	6	9	(8)	6
5-10	20 (19)	1	16	(12)	9
>10	23 (18)	8	9	(5)	11
Total	74 (64)	18	42	(29)	32

* The figures in parentheses indicate the number of patients who had several recordings.

The data derived from Table 4 are set out graphically in Figure 1.

The cases of less than five-years' standing (Blocks *2* and *3*) are not essentially different from the entire series (Block *1*) with regard to the incidence and distribution of the electroencephalographic abnormalities. One is struck by the small number of normal electroencephalograms, and the frequent dysrhythmia and alterations in the latter among the cases of 5-10-yr. standing (Block *4*), as compared with those of more than 10-yr. standing (Block *5*).

This phenomenon, however, must be assessed also on the basis of the varying activity of the disease in the two periods:

Duration of Disease, Yr.	−/+ Activity	One or More Outbursts
5-10	21%	63%
>10	44%	33%

It will be seen from Table 5 that the electroencephalographic changes are determined by the varying activity during the two periods, rather than simply by the duration of the disease.

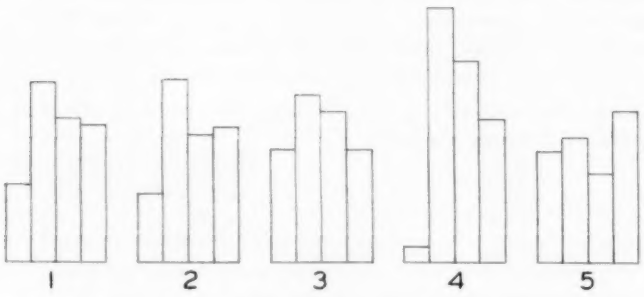

Fig. 1.—Duration of the disease in relation to the electroencephalogram.

Block *1* represents the total series; Block *2*, patients ill less than 2 yr.; Block *3*, patients ill 2 to 5 yr.; Block *4*, patients ill from 5 to 10 yr., and Block *5*, patients ill more than 10 yr.

The four columns of each block indicate the incidence of abnormal electroencephalograms, expressed in percentages of the total number of patients (in the case of "altered dysrhythmia," the number of reexamined patients). Column 1 represents the normal electroencephalogram; Column 2, altered dysrhythmia; Column 3, general dysrhythmia, and Column 4, phase reversals.

TABLE 5.—*Relation of Disease Activity to Electroencephalographic Pattern*

	Total Patients	Normal EEG	General Dysrhythmia	Altered Dysrhythmia	Phase Reversals
−/+ activity	20	6	10	5	8
One outburst	18	3	11	9	7
Several outbursts	16	1	12	10	10
Classification doubtful	10	2	7	5	5
Total	64	12	40	29	30

The data from Table 5 are set out graphically in Figure 2, which shows that the number of normal electroencephalograms decreases with increasing disease activity in the course of the electroencephalographic observation period. At the same time, a larger proportion of the patients show general dysrhythmia, and the latter undergoes more alterations. As in Table 4, there does not appear to be a

definite difference in the incidence of phase reversals in the individual groups, although their incidence appears to be relatively higher among patients with a history of more than one outburst during the observation period.

The absence of influence of the duration of the disease and the general disablement on the electroencephalogram, as compared with the influence of the frequency of outbursts, indicates that the electroencephalographic abnormalities in multiple sclerosis, particularly dysrhythmia, are not caused by past pathological lesions themselves, but that, rather, they reflect processes which result in plaque formation.

Brain-Stem Symptoms.—During the observation period about half the patients exhibited lesions of the brain stem, manifesting themselves as symptoms of functional loss referable to the third to the seventh cranial nerves, often accompanied with acoustic and vestibular disturbances. The disturbances in the extremities coexisting with these brain-stem symptoms are marked by incoordinations rather than by symptoms referable to the pyramidal tract.

Normal electroencephalograms were found in only a few of the cases with lesions of the brain-stem thus manifested. Unlike the clinical-electroencephalo-

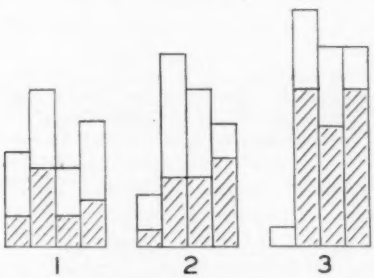

Fig. 2.—Relation of disease activity to the electroencephalographic abnormality. Columns are designated according to the scheme used in Figure 1. The cross-hatched areas indicate the number of patients, expressed in percentages, who presented "brain-stem symptoms" at the time of the examination. (The significance of these symptoms will be discussed later.)

Block *1* indicates no or minor activity; Block *2*, one outburst; Block *3*, several outbursts.

TABLE 6.—*Brain-Stem Symptoms in Relation to the Electroencephalographic Abnormalities*

	Total Patients	Symptoms Referable to Third-Seventh Cranial Nerves		Symptoms Referable to Extremities, with Coordinative Predominance
		+	−	
Normal EEG	18 (24%)	4 (11%)	14 (36%)	2 (10%)
General dysrhythmia....	42 (57%)	21 (60%)	21 (54%)	15 (75%)
Phase reversals	32 (43%)	21 (60%)	11 (28%)	9 (45%)
Total.....	74 (100%)	35 (100%)	39 (100%)	20 (100%)

graphic relations described above, the abnormalities are apparently in the form of phase reversals rather than of dysrhythmia.

The numbers involved are too small to allow of definite conclusions. A detailed examination of the case histories, however, appears to show that the occurrence of phase reversals is to a great extent related to outbursts in which the above-mentioned cranial-nerve symptoms occur.

Some luck is required to obtain tracings at the most appropriate point in the clinical course (immediately before, during, and after an outburst). In 27 cases, however, it was possible to make a direct comparison of the clinical and the electroencephalographic course. There was an apparently unmistakable parallelism in 11 of these 27 cases; a somewhat more doubtful, but probable, parallelism in 8, and no parallelism in 8 others.

Of the 64 patients who had several tracings, 12 exhibited no abnormality in any of a total of 33 electroencephalograms. Of these 12 patients, however, 4 showed unmistakable clinical activity, but symptoms referable to the brain stem of the nature mentioned occurred in only 1.

TABLE 7.—*Acoustic and Vestibular Findings in Relation to the Electroencephalogram*

	Total	Hearing		Vestibular Function	
		Normal	Impaired	Normal	Abnormal
Normal EEG	14 (22%)	13 (25%)	1 (8%)	12 (27%)	2 (11%)
General dysrhythmia	33 (52%)	25 (48%)	8 (67%)	22 (49%)	11 (58%)
Phase reversals	29 (45%)	22 (42%)	7 (58%)	18 (40%)	11 (58%)
Total	64 (100%)	52 (100%)	12 (100%)	45 (100%)	19 (100%)

TABLE 8.—*Relation of Symptoms Referable to the Medulla Oblongata and the Pons and Electroencephalographic Abnormalities of Predominantly Occipital Localization in Thirty-Nine Patients*

	Symptoms Referable to the Trigeminal and/or Facial and/or Cochlear Nerves	
	+	−
Preponderance of occipital EEG abnormalities	23 (70%)	16 (39%)
Phase reversals only	15	8
Phase reversals + general dysrhythmia	5	1
Dysrhythmia only	3	7
No particular occipital preponderance	10 (30%)	25 (61%)
Total	33 (100%)	41 (100%)

The cross-hatched areas in Figure 2 illustrate the increased involvement of the brain stem in the process with an increasing disease activity in relation to electroencephalographic abnormalities.

A total of 64 patients with no history of disease of the ear were submitted to tests of acoustic and vestibular function during the observation period (Table 7).

In Table 7, too, the numbers involved are rather small for a direct evaluation, but the tendency is the same as that shown in the relations of other functions of the brain stem to electroencephalographic abnormalities.

Symptoms referable to the trigeminal, facial, and cochlear nerves belong to the rare symptoms of a disseminated disease which allow of some conclusions regarding the localization of the underlying lesions (medulla oblongata and pons). The areas concerned receive their blood supply from the vertebral arteries, particularly the basilar artery, which also supplies the cerebellum, the greater part of the temporal lobes, and the entire occipital lobes.

In 39 patients the electroencephalographic abnormalities were predominantly occipital (Table 8).

Of the 23 cases in which occipital preponderance was observed, 16 allow of a comparison of the electroencephalographic and the clinical course.

Manifestation of EEG Abnormalities	Cases
Simultaneously with onset of symptoms	8
In close relation to their onset	3
Without any time relation to their onset	5

On the whole, there was a rather decided tendency to occipital preponderance of electroencephalographic abnormalities, particularly phase reversals, simultaneously with the manifestation of clinical symptoms referable to the medulla oblongata and pons.

COMMENT AND REVIEW OF LITERATURE

We have succeeded in finding only eight reports of electroencephalographic findings in multiple sclerosis, only three of which, however, are based on major series and none on continuous examinations.

Berger [6] described an abnormal electroencephalogram in a case of multiple sclerosis with severe mental changes. Lemere,[7] cited by Zeifert,[8] studied 18 cases, 5 of which he rejected because of psychiatric abnormalities. In 8 of the remaining 13 cases he found "poor rhythms." In their "Atlas of Electroencephalography," Gibbs and Gibbs [9] stated that scattered slow waves may occur in some cases of multiple sclerosis, whereas in many severe cases the electroencephalogram is normal. Among six subjects, Freeman,[10] and Freeman and Cohn [11] found only one abnormal electroencephalogram, which became normal during a remission.

Hoefer and Guttman,[12] in a study of 107 cases, found definite electroencephalographic abnormalities in 44%, i. e., diffuse abnormalities in 21.5%, and diffuse abnormalities with focal signs in 22.5%. Focal abnormalities occurred in more than one-half the cases with monoplegia or hemiplegia. Repeated electroencephalograms in 10 cases showed a tendency to normalization with clinical remission of the disease.

Zeifert,[8] in a study of 34 cases, found electroencephalographic abnormalities in 62%, in half of which there were focal abnormalities. His tables do not give the impression of much agreement between the distribution of symptoms and the electroencephalogram. Only two patients were followed up.

Among 47 patients with electroencephalograms, Jasper, Bickford, and Magnus [13] found definite abnormalities in 7 of 8 patients during an acute exacerbation, in

6. Berger, H.: Über das Elektrenkephalogramm des Menschen, Arch. Psychiat. **94**:16, 1931.

7. Lemere, F.: The Significance of Individual Differences in the Berger Rhythm, Brain **59**:366, 1936.

8. Zeifert, M.: The Electroencephalogram of Multiple Sclerosis, Arch. Neurol. & Psychiat. **60**:376 (Oct.) 1948.

9. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings Co., 1941.

10. Freeman, W.: Frontiers of Multiple Sclerosis, M. Ann. District of Columbia **13**:1, 1944.

11. Freeman, W., and Cohn, R.: Electroencephalographic and Pneumoencephalographic Studies of Multiple Sclerosis, Arch. Neurol. & Psychiat. **53**:246 (March) 1945.

12. Hoefer, P. F. A., and Guttman, S. A.: The Electroencephalogram in Multiple Sclerosis, Tr. Am. Neurol. A. **70**:70, 1949.

13. Jasper, H.; Bickford, R., and Magnus, O.: The Electro-Encephalogram in Multiple Sclerosis, A. Res. Nerv. & Ment. Dis., Proc. (1948) **28**:421-427, 1950.

10 of 17 patients during a subacute stage, and in 8 of 22 patients during a remission. A certain number of patients showed focal slow waves. Neither did these investigators find agreement between the distribution of symptoms and the electroencephalogram. In their words, the abnormalities of the acute stage "reflect a generalized reaction of the brain to an acute local pathologic process."

The disagreement found in the three last-mentioned series may probably be explained on the basis of a difference in interpretation of the classification of borderline cases. As might be expected, the abnormalities described are by no means specific for multiple sclerosis. By way of comparison, we shall now review a few of the relatively rare electroencephalographic experiences reported in cases of other multiple demyelinating and/or inflammatory lesions of the central nervous system.

In cases of acute encephalomyelitis, Gibbs and Gibbs[9] invariably observed slow waves, which were either diffuse or more localized, suggesting a focus.

Cazzullo and Pacella[14] studied the electroencephalograms associated with experimental encephalomyelitis in 22 rhesus monkeys. As a rule, electroencephalographic abnormalities were manifest before the clinical symptoms, but persisted for some time after a clinical remission had occurred. The abnormalities were moderate. Postmortem studies showed the lesions to be predominantly of subcortical localization.

Electroencephalographic studies of single cases or of minor series of cases of meningoencephalitis and of a few cases of parainfectious and postvaccinal encephalitis have been reported by Holmgren,[15] Marsh,[16] Lindsley and Cutts,[17] and others. In the acute stage there is usually continuous slow activity, focal or generalized, and at times wave-and-spike discharges. On the whole, the changes appear to have been more prominent than those ordinarily encountered in multiple sclerosis. As a rule, the electroencephalogram is normalized during remission.

Gibbs and Gibbs[18] studied 240 cases of encephalitis of various causes. They found a direct parallelism between the gravity of the symptoms in the various stages of the disease and the degree of electroencephalographic changes, which seldom persisted longer than the clinical activity. Dysrhythmia was severest among the children, who were also more likely to have postencephalitic convulsions.

On the whole, the electroencephalograms of these somewhat related conditions appear to be directly comparable to the abnormal electroencephalograms in multiple sclerosis, when one is considering an acute exacerbation, as to both the nature of the abnormalities and their course in relation to the clinical picture.

In principle, our electroencephalographic findings seem to correspond to previous findings in multiple sclerosis. The somewhat higher incidence of abnormal recordings in our series is probably due, not to less strict criteria, but to the length of the observation period and the repeated examinations, since the abnormalities primarily seem to reflect the activity of the pathological process. We attach more importance to the occurrence of phase reversals than is usual in cases in which there

14. Cazzullo, C. L., and Pacella, B. L.: Electroencephalographic Studies on Experimental Allergic Encephalomyelitis in Rhesus Monkeys, Arch. Neurol. & Psychiat. **63**:125 (Jan.) 1950.

15. Holmgren, E. B.: EEG i några meningo-encephalitfall, Nord. med. **40**:1810, 1948.

16. Marsh, C.: Electroencephalographic Findings in Measles Encephalitis, Bull. Los Angeles Neurol. Soc. **13**:15, 1948.

17. Lindsley, D. B., and Cutts, K. K.: Clinical and Electroencephalographic Changes in a Child During Recovery from Encephalitis, Arch. Neurol. & Psychiat. **45**:156 (Jan.) 1941.

18. Gibbs, F. A., and Gibbs, E. L.: The Electroencephalogram in Encephalitis, Arch. Neurol. & Psychiat. **58**:184 (Aug.) 1947.

is no question of expanding lesions. Unlike previous investigators, we interpret our findings as evidence at any rate of some correlation between the distribution of the symptoms and the electroencephalographic abnormalities.

When discussing the causal relationship of the electroencephalographic abnormalities, one must pay regard to function, as well as to localization, and the evaluation is complicated in both respects.

The present continuous analysis of the clinical course revealed a higher morbid activity than that recorded in previous studies, which presumably have been based, rather, on a retrospective estimation of the course (Müller[19] and Putnam and associates[20]). This activity reaches beyond the pronounced monosymptomatic or plurisymptomatic outbursts, of actual importance to the occupational capacity, and need not be recognized by the patient. It may be revealed, for example, by tests of facial sensibility or acoustic function repeated at regular intervals. To this morbid activity may be added activity in the clinically "silent zones" of the central nervous system, particularly in the cerebral hemispheres.

In multiple sclerosis, the number of plaques exceeds that of the symptoms, and in advanced cases hardly any part of the central nervous system is spared. In view of this fact, one might perhaps expect electroencephalographic abnormalities in all advanced cases. The present studies, however, have shown that the duration of the disease and the general disability do not decide the frequency or gravity of the electroencephalographic abnormalities, and that extensive dissemination is compatible with a normal electroencephalogram—at any rate, in a stationary phase of the disease.

It is generally accepted that the electroencephalogram reflects mainly the electrical activity of the cortex. In multiple sclerosis the white matter is far oftener, and more severely, involved than the cortex, although cortical involvement is by no means rare.

Sometimes the gyri are atrophic on gross inspection, and sometimes they exhibit localized areas of arachnoiditis in sites where the plaques reach the surface, at times covered by more diffuse leptomeningitic changes. The latter were first pointed out by Borst,[21] and their presence has later been confirmed by some investigators and repudiated by others. The changes in the cerebrospinal fluid in multiple sclerosis, however, indicate at least transitory meningeal involvement in, or reaction to, the pathological lesions.

Dawson,[22] who studied the cortical plaques most thoroughly, distinguished two varieties: (1) the commoner, extension of plaques from the underlying white matter to the cortex, and (2) the rarer, plaques confined to the cortical gray matter. Subsequent reports, mainly casuistic, have not shaken these fundamentals. Failure

19. Müller, R.: Studies on Disseminated Sclerosis with Special Reference to Symptomatology, Course, and Prognosis, Acta med. scandinav. (Supp. 222) **133**:1, 1949.

20. Putnam, T. J.; Chiavacci, L. V.; Hoff, H., and Weitzen, H. G.: Results of Treatment of Multiple Sclerosis with Dicoumarin, Arch. Neurol. & Psychiat. **57**:1 (Jan.) 1947.

21. Borst, M.: Zur pathologischen Anatomie und Pathogenese der multiplen Sklerose, Beitr. path. Anat. **21**:308, 1897.

22. Dawson, J.: The Histology of Disseminated Sclerosis, Tr. Roy. Soc. Edinburgh **50**:517, 1916.

to find cortical plaques apparently is often due to omission of Nissl staining. According to Brain,[23] the demyelinated areas in the cortex are of the same typical perivascular localization as elsewhere.

Cerebral atrophy, causing symmetrical or asymmetrical ventricular dilatation, is a common finding, both post mortem and in the pneumoencephalogram. In addition, Freeman [10] has emphasized the occurrence of subarachnoid focal air shadows above the convexities. Presumably, he is right in considering this retraction a result of subcortical processes, although his premise—a normal electroencephalogram in multiple sclerosis—is wrong.

A possible cortical atrophy, occurring in a small or moderate number of cases, is an unsatisfactory explanation of the electroencephalographic abnormalities described above. It must be borne in mind that we are dealing with a condition the great events of which have been proved, by clinical, as well as pathological, studies, to leave their traces in the hemispheres, the brain stem, and the spinal cord.

Subcortical plaques of sclerosis may produce disturbance in the supply of blood to the overlying cortex, and thereby also in the cortical function, which is reflected in the electroencephalogram. The same plaques may affect the projection fibers, thereby altering the electrical activity in a limited area of the cortex. The electroencephalogram cannot localize the depth of the processes causing focal abnormalities.

O'Leary and Fields,[24] in a study of 209 convulsive subjects, selected either because their electroencephalograms or their convulsions were "focal," were unable to distinguish between focal cortical and focal subcortical lesions on the basis of the electroencephalograms.

The theta rhythm (4 to 7 cps), which is relatively common also in cases of multiple sclerosis, has been ascribed by Walter [25] to subcortical processes. Unable to confirm this hypothesis, Kershman and others [5] stated that this frequency is almost as common in cases of meningeal tumors as in those of subcortical astrocytomas.

In cases of stationary cerebral atrophy, the activity of lowest frequency, possibly with small amplitudes, is usually found over the most damaged hemisphere (Frey [26]).

The relationship of the electroencephalogram to lesions in the brain stem and the spinal cord is even more doubtful.

Plaques in the medulla oblongata and the pons are comparatively small and well defined, except in cases of "acute multiple sclerosis." Analysis of the clinical course indicates that several plaques arise at the same time. The comparatively rapid remission of symptoms referable to such plaques—not including facial paralysis—can hardly be attributed exclusively to pathoanatomical regression and a particularly rapid restitution of neuronal function. In assessing the remission, one must not forget the possibility of relatively ample compensation, at any rate within the field

23. Brain, W. R.: Critical Review: Disseminated Sclerosis, Quart. J. Med. **23**:343, 1930.

24. O'Leary, J., and Fields, W. S.: Focal Disorders of Brain Activity as It Relates to the Character of Convulsive Seizures: Electroencephalogram in Focal Seizures, Arch. Neurol. & Psychiat. **62**:590 (Nov.) 1949.

25. Walter, W. G.: Discussion on the Electroencephalogram in Organic Cerebral Disease, Proc. Roy. Soc. Med. **41**:237, 1948.

26. Frey, T. S.: Klinisk electroencephalografi, Nord. med. **40**:1805, 1948.

of acoustic and vestibular function. In our material, electroencephalographic abnormalities were relatively common in the presence of symptoms ascribed to the brain stem (but, of course, it cannot be ruled out that plaques in the hemisphere which affect projection fibers to the brain stem may share the responsibility).

The present series includes cases illustrating how dysrhythmia may be provoked by outbursts which from the clinical point of view are "purely" medullary. Considering, however, that most outbursts are probably plurisymptomatic, and not forgetting the "silent" plaques in the hemispheres, one cannot, without further study, take such examples as evidence of antidromic impulses in the pyramidal tracts.

In 15 cases of various lesions of the spinal cord, such as tumor and arachnoiditis, Kaplan and Stearns [27] found (predominantly central and precentral) electroencephalographic abnormalities. Referring to Woolsey and Chang's [28] paper on antidromic volleys, they advanced the hypothesis that electrochemical changes occurring mainly in the slowly progressing lesions caused antidromic impulses in the pyramidal tract and, consequently, the localized electroencephalographic abnormalities observed.

The electroencephalographic findings of Merlis and Watson [29] in 18 cases of transverse lesions of the cord are in direct conflict with those of Kaplan and Stearns. The latter's theory is also opposed by studies of Pacella and associates,[30] in 18 cases of paralysis due to poliomyelitis, despite the different nature of the pathological lesions. The only two patients showing marked electroencephalographic abnormalities had presumably had polioencephalitis.

According to Jasper, Bickford, and Magnus [13] changes in the electroencephalograms of multiple sclerosis "might be expected, if lesions in certain critical areas of the brain stem were such as to be reflected in general alterations in cortical activity."

In evaluating the causal relation of the electroencephalographic findings in the case of a lesion predominantly accompanied with periventricular sclerosis, and often with thalamic involvement, it is reasonable to mention Murphy and Gellhorn's [31] experimental demonstration of the hypothalamic origin of the alpha rhythm. Finally, it is not out of place to call attention to Jasper's [32] experiments. In the cat, he was able to produce 8 to 12 cps waves (almost indistinguishable from those which occur spontaneously, and most likely analogous to the alpha rhythm of the human electroencephalogram) by the administration of a single electrical pulse to the reticular system of the thalamus.

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27. Kaplan, L. I., and Stearns, E.: Electroencephalographic Studies in Spinal Cord Disease, Arch. Neurol. & Psychiat. **62**:293 (Sept.) 1949.

28. Woolsey, C. N., and Chang, H. T.: Cortical Origin of the Pyramidal Tract as Defined by Antidromic Volleys from the Medullary Pyramid, Federation Proc. **6**:1, 1947.

29. Merlis, J. E., and Watson, C. W.: The Electroencephalogram After Injury to the Spinal Cord in Man, Arch. Neurol. & Psychiat. **61**:695 (Sept.) 1949.

30. Pacella, B. L.; Jungeblut, C. W.; Kopeloff, N., and Kopeloff, L. M.: The Electroencephalogram in Poliomyelitis, Arch. Neurol. & Psychiat. **58**:447 (Oct.) 1947.

31. Murphy, J. P., and Gellhorn, E.: Influence of Hypothalamic Stimulation on Cortically Induced Movements and on Action Potentials of the Cortex, J. Neurophysiol. **8**:341, 1945.

32. Jasper, H.: Diffuse Projection Systems: The Integrative Action of the Thalamic Reticular System, Electroencephalog. & Clin. Neurophysiol. **1**:405, 1949.

Because of the multitude of lesions in multiple sclerosis, and because of their only partly destructive character, involving a possibility of partially preserved neuronal function, one may anticipate finding only tendencies to, and, not convincing evidence of, a correlation of the electroencephalographic findings and the localization of cerebral function.

Although we are unable to rule out morbid activity in a clinically stationary phase, the electroencephalographic abnormalities were most conspicuous in the presence of clinical activity and changed with the latter. Presumably, the activity recorded by the electroencephalogram is mainly localized in the cerebral hemispheres. Possibly, the tracing represents a more or less generalized cerebral reaction to the development of a localized pathological lesion.

Dysrhythmia may be diffuse, but in about two-thirds of our patients there was either a difference between the two hemispheres or occipital preponderance. The greater part of the transitory phase reversals were of occipital localization, and apparently related to the development of symptoms which may be reasonably ascribed to lesions in the medulla oblongata and the pons. This finding may perhaps be interpreted to the effect that a generalized cerebral reaction to the pathological lesions is particularly reflected within the common area of vascular supply. Possibly, it means that a regular dissemination of lesions within each individual outburst is to some extent confined to a given vascular area.

It is difficult to decide to what extent the persistent electroencephalographic abnormalities reflect direct cortical damage, and to what extent they are a result of stationary subcortical lesions leading to an indirect alteration of the cortical activity.

SUMMARY AND CONCLUSIONS

A total of 203 electroencephalograms obtained from 74 patients with multiple sclerosis were studied. For 64 patients more than one tracing was obtained, the average being three records in the course of an average observation period of nine months.

At the same time, the patients underwent clinical examinations at intervals of about one month. (The electroencephalograms were interpreted without a knowledge of the clinical status.)

This continuous analysis revealed a higher morbid activity than is ordinarily reported in multiple sclerosis. In addition to minor changes in the symptoms, referable mainly to cranial nerves, more than half the patients had one or more definite outbursts, resulting in a pronounced change in their ability in the course of the nine months. The activity was lowest in patients with long-standing disease.

Electroencephalographic abnormalities occurred in three-fourths of the patients who had one electroencephalogram and in four-fifths of those examined repeatedly.

Slight, more rarely, moderate, dysrhythmia (according to the ordinary criteria) occurred in 63% of patients. The severity of this sign varied in the course of the observation period in 73%, whereas it remitted completely in 15%. The dysrhythmia was in most cases diffuse, but showed focal preponderance in about two-thirds of the patients.

Transitory, usually unilateral, migrating phase reversals were observed in 47% of patients. The relation to the clinical course supports the significance of this transitory phenomenon.

Except for being related to the varying morbid activity in the different periods, the electroencephalographic findings did not appear to have any bearing on age, degree of disablement, or duration of the disease.

With increasing activity of the disease, the number of normal electroencephalograms decreased from 30% to 6%; the incidence of dysrhythmia increased from 50% to 75%, and the incidence of phase reversals increased from 40% to 64%. These findings seem to indicate that the electroencephalogram reflects the morbid activity rather than the number and localization of past pathological processes. (Extensive dissemination appears to be compatible with a normal electroencephalogram in a clinically stationary phase. An outburst clinically confined to the cord may be reflected in the electroencephalogram.)

Clinically manifest brain-stem activity (symptoms of functional loss from the third to the eighth cranial nerves in one-half the patients) is virtually always reflected in the electroencephalogram, comparatively often in the form of phase reversals.

There was occipital preponderance of the electroencephalographic abnormalities in 70% of the patients with clinically manifest involvement of the medulla oblongata and the pons (trigeminal, facial, and cochlear nerves). Possibly, this occipital predominance indicates that any generalized cerebral reaction to the lesions is reflected particularly within the common area of blood supply (in this case, the basilar artery and its branches), or that a regular dissemination of lesions within the individual outburst is to some extent confined to a given vascular area.

Our findings are compared with the earlier, comparatively few electroencephalographic observations in cases of multiple sclerosis and kindred disseminated demyelinating and/or infectious diseases.

The applicability of the electroencephalogram in determining the nature and localization of the lesion (cortex, subcortical white matter, brain stem, spinal cord) is discussed on the basis of previous and present findings.

It is considered likely that the more persistent cortical dysfunction recorded in the electroencephalogram of multiple sclerosis is due to mainly subcortical sclerotic plaques directly damaging projection fibers, or perhaps causing ischemic anoxia.

In addition to the correlation of the electroencephalogram and the disease activity, particularly the symptoms referable to the brain stem, a clinical-electroencephalographic correlation is apparent in cases of cerebral paroxysm and of dementia. This aspect will be dealt with in more detail in a later paper.

Not much diagnostic significance is attributed to the electroencephalogram except that an electroencephalographic abnormality occurring in a case of clinically isolated medullary outburst may indicate dissemination of the lesion.

By recording the morbid activity, the electroencephalogram may contribute to evaluation of the effect of attempts at causal treatment of the disease. It is not permissible, however, for one to draw definite conclusions from a single electroencephalographic record, since it is to some extent influenced by past pathological processes.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

EVALUATION OF CURARIZING AGENTS IN MAN. K. R. UNNA, E. W. PELIKAN, D. W. MACFARLANE, R. J. CAZORT, M. S. SADOVE, and J. T. NELSON, J. A. M. A. **144**:448 (Oct. 7) 1950.

Agents intended for curarizing effects in therapy can be evaluated accurately only on man himself by quantitative observations, unobscured by the effects of an anesthetic or any other drug. More than 150 experiments were performed by the authors on six normal male volunteers, ranging in age from 22 to 36 and in weight from 150 to 180 lbs. (68 to 81.6 kg.).

It was found that in potency, as determined by the effect on strength of grip, decamethonium bromide (decamethylenebis-[tetraethylammonium bromide], syncurine,® or C10) surpasses all other agents. The variability in response to decamethonium bromide is greater than that to either tubocurarine chloride or dimethyl-tubocurarine iodide.

The threshold of the repiratory muscles to the paralyzing effects is significantly different for each drug. It is lowest to decamethonium bromide and highest to dimethyl-tubocurarine iodide and flaxedil® (1,2,3-tri[diethylaminoethoxy] benzene triethyl iodide).

Duration of action is shortest with dicamethonium and flaxedil,® intermediate with dimethyl-tubocurarine iodide, and longest for tubocurarine chloride.

Repeated doses of the two last-mentioned drugs are cumulative when given at intervals of 45 minutes, even after recovery from measurable effects. Repeated doses of decamethonium bromide are not cumulative but have, on the contrary, a decreased effect on the musculature.

Neostigmine methylsulfate mitigates, but does not completely abolish, the effects of a subsequent injection of tubocurarine chloride. No effective antidote to decamethonium bromide in man is known.

Pretreatment with tubocurarine chloride diminishes greatly the curarizing effects of a subsequent injection of decamethonium bromide.

ALPERS, Philadelphia.

THE UPTAKE OF GLUTAMIC ACID AND GLUTAMINE BY BRAIN AND OTHER TISSUES OF THE RAT AND MOUSE. P. SCHWERIN, S. P. BESSMAN and H. WAELSCH, J. Biol. Chem. **184**:37, 1950.

The authors believe that it may be of considerable biologic significance that, as shown in their experiments, glutamine enters the liver, and probably the brain, with greater ease than does the parent amino acid. While glutamic acid or its keto acid takes part in many of the basic metabolic reactions (oxidative deamination, entrance of ammonia into the amino-acid pool, transamination, etc.), the amide is inert in all these processes. It represents, therefore, a store of the metabolically highly active amino acid and keto acid, from which they can be liberated easily by enzymatic action. While a change in glutamic acid or ketoglutaric acid may influence the rate of such basic metabolic mechanisms as the tricarboxylic-acid cycle or transamination, a change in glutamine concentration will not affect the rate of these processes. The determination of glutamic acid and glutamine in the protein-free filtrates of brain, muscle, liver, and kidney of rats and mice with the aid of a microchemical method is described. In the whole brain of these animals, as well as in the brain of cattle, sheep, rabbits, cats, and pigeons, free glutamic acid occurs in a concentration of about 0.01 mole, and glutamine, of about 0.004 mole, per kilogram. Kidney contains a large excess of the amino acid over the amide, while in liver the concentrations of the two compounds are about equal. The changes in concentration of glutamic acid and glutamine in blood, liver, muscle, kidney, and brain were determined at various intervals up to one hour after the intravenous administration of the two compounds in rats and mice. Both amino acids disappear rapidly from the blood. After the administration of the amide, large amounts of it are taken up by the liver. The rise in amide concentration in the liver is accompanied with the liberation of glutamic acid. After administration of glutamic acid, its increase in liver and muscle may be explained by the equilibration of the blood-plasma

concentration with that of the extracellular-fluid phase. There was a considerable accumulation in the kidney of both compounds after the administration of either one; when an excess of glutamine was present, glutamic acid was liberated. No significant increase in the glutamic-acid or glutamine concentration of the brain followed the injection of glutamic acid. The results of the experiments in which the amide was administered suggest that glutamine may enter the brain. The significance of the results with respect to brain metabolism and the function of glutamine is discussed.

PAGE, Cleveland.

OBSERVATIONS CONCERNING THE PRODUCTION AND EXCRETION OF CHOLESTEROL IN MAMMALS. I. PLASMA CHOLESTEROL AFTER BILE DUCT LIGATION AND FREE CHOLESTEROL INJECTION. S. O. BYERS, M. FRIEDMAN, and F. MICHAELIS, J. Biol. Chem. **184**:71, 1950.

The concentration of free and esterified cholesterol in the blood plasma of rats subjected (*a*) to ligation of the bile duct or (*b*) to ligation of the bile duct followed by a single intravenous injection of a free-cholesterol suspension was observed at intervals of 6, 24, and 72 hours after ligation. It was found that simple ligation of the bile duct alone affected a rapid and great increase in the free cholesterol of plasma, with a much slower and slighter rise in esterified cholesterol. Animals with ligation of the bile duct followed by injection of free cholesterol showed a greater rise in free cholesterol. The injected excess cholesterol did not affect the rate of increase of free cholesterol attributable to the biliary obstruction, but remained as a fixed increment superimposed on the sustained rise which results from simple obstruction. The possibility is suggested that regulation of the free-cholesterol level in the plasma of the rat is dependent on its destruction or excretion by the hepatobiliary system.

PAGE, Cleveland.

LOSS OF NERVE CELLS IN EXPERIMENTAL CEREBRAL CONCUSSION. R. A. GROAT and J. Q. SIMMONS, J. Neuropath. & Exper. Neurol. **9**:150 (April) 1950.

Concussion may be described as a discrete, traumatic cerebral affliction. It may occur as an uncomplicated phenomenon, and as such may be reversible or, in animals and presumably in man, irreversible, terminating in death. It can, in addition, prevail as a complication in the more overt forms of brain injury, and here, likewise, it may be reversible, or it may be the sole or a contributing cause of death.

In this study nerve cells were counted in selected brain-stem areas of control guinea pigs and guinea pigs in which concussion had been induced by a single blow to the head 13 months prior to killing of the animals. A considerable cell deficit was disclosed in the injured animals in the reticular formation, the lateral vestibular nucleus, and the red nucleus. These are groups in which immediate change in the pattern of Nissl substance, and subsequent chromatolysis, follow the blow. No loss was indicated from either the motor trigeminal nucleus or the abducens nucleus, and no cytological alterations were evident in these nuclei early in concussion. No other changes were observed.

Groat and Simmons give reasons in support of a tenet that there is a regional differential of intensity of concussive action, which, however, is compatible with the generalized nature of the injury. Both the degree of early chromatolysis in a nucleus and the degree of nerve-cell loss there are proportional to the intensity of concussive action, and hence to each other; but more cells are lost from a nucleus than appear severely affected there in brains in which chromatolysis is at its height. Since the early chromatolysis is widely distributed among interneuron groups of the brain stem, the cell loss demonstrated by the counts becomes an indicator of a more extensive nerve-cell deficit. Moreover, it is evident that some cell loss will occur in all concussion, even in extremely light ones, and in some subconcussions, and that cell losses greater than those demonstrated will occur in severer concussions.

ALPERS, Philadelphia.

NEUROLOGICAL EFFECTS OF OXYGEN IN CHRONIC COR PULMONALE. C. E. DAVIES and J. MACKINNON, Lancet **2**:883 (Nov. 12) 1949.

Davies and Mackinnon report their experience with two cases of cor pulmonale in which neurological disturbances developed after the administration of oxygen. The first man experienced myoclonic movements, profuse sweating of the head and neck, and a sense of fulness of the

head. The second man became comatose and died two hours after the administration of oxygen and carbon dioxide. Autopsy revealed subarachnoid hemorrhage with engorgement of the small vessels and capillaries.

A study was made of the effect of inhalation of oxygen on the cerebrospinal fluid pressure in four more cases of cor pulmonale and in five control cases. In all four cases of cor pulmonale the pressure rose with the inhalation of oxygen. When air was substituted for oxygen, the pressure dropped. In none of the control cases did the intrathecal pressure rise. The authors suggest that the changes in spinal fluid pressure in cor pulmonale after giving of oxygen are linked with changes in the metabolism of carbon dioxide.

MADOW, Philadelphia.

PARTIAL RETENTION OF AUTONOMIC FUNCTION AFTER PARAVERTEBRAL SYMPATHECTOMY. J. D. BOYD and P. A. G. MONRO, Lancet **2**:892 (Nov. 12) 1949.

During an investigation of the effect of thoracolumbar sympathectomy on autonomic function, Boyd and Monro observed that an "escape" area of sweating constantly persisted in the lower part of the abdomen and the front of the thighs, corresponding to the first and second lumbar segmental dermatomes, and possibly including the 12th thoracic and the third lumbar. They examined a large number of human embryos in an attempt to locate the autonomic cells of the residual pathway. This investigation revealed the presence of numerous "intermediate" sympathetic ganglia, of varying size and distribution, in the course of the rami communicantes passing between the lumbar sympathetic ganglia and the corresponding anterior primary rami of the lumbar nerves. The intermediate ganglia were situated dorsal to the psoas muscle or between its posterior fibers of origin. They were on the course of the more dorsal of the rami communicantes of the first, second, and third lumbar nerves. The position of many of these intermediate ganglia was such that they would necessarily escape removal in the usual operation of thoracolumbar sympathectomy.

One of the patients previously checked for autonomic function following thoracolumbar sympathectomy, and found to have the sudomotor escape pattern, was also found at autopsy to have many intermediate ganglia in the rami communicantes and primary divisions of the first and second lumbar nerves.

MADOW, Philadelphia.

DEPARTURE OF SUBSTANCES FROM THE SPINAL THECA. F. HOWARTH and EUGENIA R. A. COOPER, Lancet **2**:937 (Nov. 19) 1949.

Howarth and Cooper studied the possible routes of departure of radioactive substances injected into the fluid in the lower spinal canal of cats. Three possibilities were proposed: (1) ascent into the cranial subarachnoid space with subsequent absorption into the venous sinuses via the arachnoid villi; (2) removal via the lymphatic drainage of the spinal subarachnoid space; (3) direct passage into the local venous drainage of the spinal theca.

To test the first theory, radioactive substances were introduced by lumbar puncture, and spinal fluid was collected both from the lumbar theca and from the cisterna magna. The concentration dropped to approximately 10% in the lumbar theca but rose a minute amount in the cisternal space. Blood samples drawn from the veins most likely to drain the spinal subarachnoid space, however, including the vertebral, the internal and external jugular, the inferior and superior venae cavae, and the azygos, revealed an immediate appearance in the venous circulation of the radioactive material injected into the lumbar theca, with the highest concentration found in the azygos vein. The authors conclude that in the cat the venous channels are a direct route of drainage from the spinal subarachnoid space.

MADOW, Philadelphia.

SUPRAVITAL ANALYSIS OF DISORDERS IN THE CEREBROVASCULAR PERMEABILITY: III. A CRITICAL ANALYSIS OF THE TECHNIQUE AND RESULTS OBTAINED IN EXPERIMENTAL ANIMALS. T. BROMAN, Acta psychiat. et neurol. **25**:19, 1950.

Experiments were performed on animals to analyze the conditions necessary for a supravital examination of the permeability of the cerebral vessels. Broman points out and analyzes the various sources of error and the disturbing factors that might adversely affect the results. He points out that the examination should be performed as soon as possible after death. The

dye solution must be properly washed out before fixation of the brain with dilute solution of formaldehyde U. S. P. If the brain is subjected to traumatic injury after death, the vessels will rupture and the dye escape. An elevated temperature, if extreme, may cause a disturbance in the permeability of the cerebral blood vessels.

ALPERS, Philadelphia.

Neuropathology

NEUROPATHOLOGICAL FINDINGS IN PHENYL-PYRUVIC OLIGOPHRENIA (PHENYL-KETONURIA). E. C. ALVORD, L. D. STEVENSON, F. S. VOGEL, and R. L. ENGLE JR., J. Neuropath. & Exper. Neurol. **9**:298 (July) 1950.

Phenylpyruvic oligophrenia (phenylketonuria) is a disease characterized by three constant features: mental deficiency (of the idiot or imbecile grade), excretion of phenylpyruvic acid in the urine, and recessive Mendelian inheritance by a single autonomal gene, neither linked to sex or eye.

In this study an examination was made of the central nervous system in five cases. The authors cite evidence to show that the disease is due to a metabolic error contingent on the recessive inheritance of a defect in an enzyme that converts phenylalanine to tyrosine.

In two cases a prominent lack of myelination of the nervous system involving principally the optic, corticospinal, corticopontocerebellar, and perhaps other tracts, and positions of the peripheral nervous system, was found in siblings 16 and 28 months of age. In another case, that of an adult, a defect in myelination was noted in the optic chiasm; in two other cases, also of adults, no such change appeared anywhere. Other abnormalities, however, such as gliosis and increase of fat about blood vessels, were present in all five cases; this was especially pronounced and was accompanied with numerous rod-shaped microglia cells in one case. Alvord and associates raise the question whether the retardation in myelination may be responsible, at least in part, for the mental deficiency.

ALPERS, Philadelphia.

Meninges and Blood Vessels

MENINGITIS DUE TO SIMULTANEOUS DOUBLE INFECTIONS IN CHILDREN. E. B. VADEN, E. C. RICE, and V. STADNICHENKO, J. A. M. A. **143**:1402 (Aug. 19) 1950.

Only 13 cases of meningitis due to simultaneous double infection were found in a review of the literature. The authors report 10 cases due to a simultaneous double infection in children, this number representing 8.0% of patients hospitalized in a 30-month period.

In nine of the patients Hemophilus influenzae was one of the offending organisms. The associated organisms, in order of frequency, were Neisseria intracellularis (four patients), Streptococcus (three patients), and Diplococcus pneumoniae (two patients). All patients were 5 years of age or under, five being less than 1 year of age.

In all but one patient both organisms were isolated from culture of the spinal fluid taken at the initial examination. Two organisms were seen on the original spinal-fluid smear of one patient, but only one was cultured. However, the other organism was found in both blood culture and petechial smears.

All patients were treated with sulfadiazine and penicillin, and seven also received streptomycin. Massive doses of intramuscularly administered penicillin were used in the more recent cases, this treatment appearing to shorten the course of the disease. There were no fatalities among these patients.

Because of the high incidence of double infections in this series, Vaden and his colleagues suggest that every child with purulent meningitis be treated for a mixed infection until bacteriologic studies are completed.

ALPERS, Philadelphia.

NON-TRAUMATIC THROMBOSIS OF THE CAROTID ARTERY. N. O. AMELI and D. W. ASHBY, Lancet **2**:1078 (Dec. 10) 1949.

Ameli and Ashby add six cases of nontraumatic thrombosis of the carotid artery demonstrated by angiography to the 33 cases already reported in the literature. Of these six cases, there were complete thrombosis of the common carotid artery in 1, thrombosis just above the bifurcation

in 2, a lesion of the intracranial portion of the internal carotid artery in 2, and pronounced tortuosity, narrowing, and irregularity of the lumen of the internal carotid artery in its intracranial portion in 1. The most likely cause of the thrombosis was arteriosclerosis, which was present in at least two cases, the exact cause being obscure in the others. The symptoms varied; often the first sign was transient weakness of one of the extremities, usually on the right side, associated sometimes with a minor disturbance of speech. Partial recovery usually occurred, followed by several recurrent minor episodes, culminating in a dramatic incident with increased weakness, aphasia, loss of consciousness, or visual defect. The interval between the initial episode and the major incident varied from a few hours to many years. In attempting to explain the occurrence of symptoms with thrombosis of the internal carotid artery, in contrast to the usual absence of disturbance in ligation of the artery, the authors cite the suggestion of Andrell that the attacks are due to nerve impulses arising in the wall of the diseased carotid artery, causing vasospasm of the cerebral vessels.

MADOW, Philadelphia.

Diseases of the Brain

ABDOMINAL EPILEPSY VERSUS "ABDOMINAL MIGRAINE." M. T. MOORE, Ann. Int. Med. **33**:122 (July) 1950.

It is still accepted that there exist clinical variants of common migraine, or hemicrania. Moore asserts that the term "abdominal migraine" is inappropriate and pathophysiologically incorrect. He suggests that the cases of "abdominal migraine" reported in the literature fall into two classes: (1) those which truly belong in the category of abdominal epilepsy, and (2) those in which manifestations of abdominal epilepsy occur coincidentally with the migraine syndrome or alternate with it. He indicates that the abdominal symptoms occurring in the migraine syndrome are brought about by irritation of cortical areas 6, 5, and 3 and/or the diencephalon during the vasoconstrictor, ischemic phase of the migraine episode and that this irritation, in turn, provokes abnormal intestinal motility, with resultant pain.

The author points out that if the conception of paroxysmal abdominal pain in its isolated form, or the form exhibited as an accompaniment to the migraine syndrome, is interpreted in the mechanical vascular connotations of migraine, the use of antimigrainous drugs will afford no relief, since the latter affect dilated blood vessels. If, on the other hand, the view is adopted that paroxysmal abdominal pain is an epileptic display in the migraine syndrome resulting from abnormal discharges emanating from certain ganglion cells "irritated" by the hypoxia of the ischemic, vasoconstrictor phase of the syndrome, then adequate and effective treatment can be given for this symptom. This treatment consists of use of anticonvulsant drugs and measures. Not only can the symptom of paroxysmal abdominal pain be relieved and prevented, but the excessively time-consuming, annoying, and expensive studies to which these patients are usually subjected may be avoided.

ALPERS, Philadelphia.

RELATION OF BRUCELLOSIS AND MULTIPLE SCLEROSIS. C. G. SPICKNALL, L. T. KURLAND, B. N. CARLE, and L. L. TERRY, J. A. M. A. **143**:1470 (Aug. 26) 1950.

The possible relation of brucellosis to multiple sclerosis was suggested by Kuger and Haden as the result of finding positive cutaneous reactions to Brucella antigen in 115 of 118 patients with multiple sclerosis. In view of the differences of opinion regarding the interpretation of the findings, Spicknall and his colleagues decided to evaluate the brucellosis status of 20 patients with multiple sclerosis. The evidence presented here fails to support the previously suggested impression that there is a strong and consistent relation between brucellosis and multiple sclerosis.

ALPERS, Philadelphia.

BRUCELLOSIS AND MULTIPLE SCLEROSIS. C. W. EISELE, N. B. MCCULLOUGH and G. A. BEAL, J. A. M. A. **143**:1473 (Aug. 26) 1950.

A relation between brucellosis and multiple sclerosis has recently been postulated by Kuger and Haden, who reported a high incidence of cutaneous sensitivity to Brucella antigens in patients with the diagnosis of multiple sclerosis.

Eisele and his co-workers found no evidence of a relation between brucellosis and multiple sclerosis with the use of Brucella-agglutination tests, opsonocytophagic tests, and brucellergen skin tests performed on 52 patients with multiple sclerosis.

ALPERS, Philadelphia.

POST-INFECTIOUS ENCEPHALOMYELITIS AND MULTIPLE SCLEROSIS: SIGNIFICANCE OF PREVIOUS ENCEPHALOMYELITIS. L. VAN BOGAERT, J. Neuropath. & Exper. Neurol. **9**:219 (July) 1950.

In many cases of acute disseminated encephalomyelitis the condition is much like multiple sclerosis; in others it is like postexanthematous encephalomyelitis. Of the author's 19 patients reported on between 1927 and 1932, 4 later had classic multiple sclerosis; 1 could not be followed, and 1 died in the acute stage. One had acute disseminated encephalomyelitis closely resembling, if not identical with, multiple sclerosis. Another, who survived four months, failed to show features of multiple sclerosis but, rather, manifested residuals of myelitis with small perivascular foci. Eleven patients are still living, completely free of any neurologic abnormality. Such data do not favor the theory that the majority of cases of acute disseminated encephalomyelitis represent only acute early stages of multiple sclerosis.

Two fatal cases are added, the disease in both following in the wake of nonspecific infections. The second patient was a child who had previously survived postmeasles encephalitis and in whom postexanthematous encephalomyelitis recurred, with the same clinical picture. Both of these patients showed all the histologic characteristics of perivenous or postinfectious encephalomyelitis and none of the features of acute multiple sclerosis.

These two new cases demonstrate that perivenous encephalitis gets its special character from the nature of the "terrain" in which the noxious agent operates, and not from the causative agent itself, which is variable and often not specific. It is quite likely that even serious acute disseminated encephalomyelitis may vanish completely and permanently, and from this point of view the second case is important. In the histologic picture no traces of old foci could be seen, even though there had been a similar disease three years previously.

It is quite possible that multiple sclerosis represents a reaction along the same lines, but it has not been shown, from either the clinical or the histopathologic standpoint, that multiple sclerosis is only a "transformation" of the form of reaction called perivenous encephalitis, determined by a modification of the tempo of the disease, a delay in sensitization eventuating in that form which is called multiple sclerosis.

Previous encephalitis is only one of the pathologic pictures resulting from participation of the central nervous system in nonspecific infections. Lymphocytic meningoencephalitis and cerebral purpura are two other types. At present there is no explanation, either in neuropathology or in general pathology, for the fact that following apparently identical prodromal infections there is such a great variation in the involvement of the central nervous system.

Van Bogaert concludes that the study of the disease with special regard to the tempo, variability in duration, and rhythm, in patients differing in age, constitution, and past medical histories may be very useful in the construction of the entire sequence of the pathologic changes; but at this stage of our knowledge we must accept with caution any conclusion about their reciprocal relations.

ALPERS, Philadelphia.

XANTHOMAS OF THE CHOROID PLEXUS IN MAN. A. WOLF, D. COWEN, and S. GRAHAM, J. Neuropath. & Exper. Neurol. **9**:286 (July) 1950.

Xanthomas of the choroid plexus in man are commoner than has been supposed. In a consecutive series of 1,181 autopsies in which examinations of the brain were performed, xanthomas were found in 1.6%. They occur in middle-aged or elderly persons as small, multiple, dull-yellow plaques in the glomus of the choroid plexus of one or both lateral ventricles. None encountered to date has attained sufficient size to be of clinical significance.

ALPERS, Philadelphia.

MYOCLONIA HEREDITARIA MUSCULI MENTALIS. A. YDE, Acta psychiat. et neurol. **25**:111, 1950.

Yde describes a hereditary form of myoclonia musculi mentalis which occurs both in males and in females and can be transmitted through persons of either sex. There were seven known cases of the disease in the family studied.

The symptom presented consisted of fine, but rapid, myoclonic twitchings in the region of the chin, which persisted for a few moments to half a day. Other groups of facial muscles were not involved; the myoclonic movements of the musculus mentalis did not affect the lower lip, and there were no accompanying sensory phenomena. The syndrome occurred as early as the second or third week of life and appeared independently of weeping or laughing.

ALPERS, Philadelphia.

Diseases of the Spinal Cord

EVOLUTION OF NEUROLOGIC SIGNS OF EARLY ANTERIOR POLIOMYELITIS. L. J. POLLOCK, B. BOSHES, I. FINKELMAN, F. HILLER, H. CHOR, M. BROWN, A. J. ARIEFF, E. LIEBERT, E. L. TIGAY, M. SCHILLER and I. C. SHERMAN, Am. J. Dis. Child. **79**:973 (June) 1950.

It was felt that a more accurate picture of the early stages of anterior poliomyelitis could be obtained from frequent examinations, both day and night, of a small number of patients. Thirty patients were intensively studied by 11 neurologists, rotating on tours of duty of six hours each during the day and night for 30 days.

It has been previously reported by these investigators that there is no spasm in the muscles in early anterior poliomyelitis.

In all cases of meningitis, rigidity of the neck, the direct Brudzinski sign, and the Kernig sign were found to a marked degree. In early anterior poliomyelitis these signs varied in frequency and intensity. Nuchal rigidity was rather constant, appearing in 92.4% of examinations, but the head might be flexed to a certain degree without resistance. The Brudzinski sign appeared in 37% but could be elicited from the beginning of head flexion in only 4%. The Kernig sign appeared in 39% and was most evident in the greater degrees of extension of the leg on the thigh. Both the Kernig and the Lasègue sign, especially the latter, occurred with increasing frequency as time elapsed after the onset of illness, suggesting that the cause of these signs in early anterior poliomyelitis is pain.

Severe paralysis was observed as early as 18 hours after onset. Usually weakness appeared and increased to a peak between the 75th and the 150th hour. The weakness might remain constant for a number of hours and progress to paralysis, or might diminish and again increase, to result finally in paralysis or recovery.

In muscles destined to become paralyzed the deep reflexes were absent in 91% of examinations. The earlier they disappeared, the severer was the residual paralysis. The earlier a continued absence of deep reflexes occurred, the severer the residual paralysis. As with muscle power, so with deep reflexes, there was a great fluctuation in relation to time.

When the lower extremities were destined to become severely paralyzed, the abdominal reflexes disappeared in 85% of the examinations up to the 100th hour after onset. This early absence of the abdominal reflexes was found to be a valuable prognostic sign. They were increased in 57% of examinations when no muscles were destined to become paralyzed, and in 42% when only the upper extremities were destined to become paralyzed.

The plantar reflexes were absent at various times in 35% of examinations of severely paralyzed lower extremities in which movement of the toes was still possible. They were brisk or increased in 25% of severely paretic lower extremities, in 64.5% when the lower extremities were moderately paretic, and in 85% when only the upper extremities were paretic.

In the presence of an upper-motor-neuron lesion there is a consistent relation in which hyperactive deep reflexes are associated with diminished or absent superficial reflexes and a Babinski sign. The Babinski sign was found very infrequently in this series. It was fleeting and inconstant and seemed not to be due to an upper motor neuron lesion, but was comparable to its presence in anoxia, in anesthesia, and after convulsions. When the deep reflexes were hyperactive in 57% of examinations, the abdominal reflexes were absent in only 3.2%. When, in another group, the deep reflexes were hyperactive in 91% of examinations, the abdominal reflexes were brisk in 97%. When the deep reflexes were brisk in 57% of examinations, the plantar

reflexes were hyperactive in 65%. These inconsistencies suggest that there was no evidence of any upper motor neuron lesions in these cases.

Direct myotatic irritability was increased predominantly in the muscles of the upper extremities, being greater in paralyzed than in unparalyzed muscles. The increased irritability was related particularly to time after onset, being greater early and disappearing late after onset. No consistent correlation could be found with the degree of paralysis. In this regard, the paralyzed muscle, by not becoming irritable to mechanical stimuli, performed as it does with electric stimuli. A comparable state obtains in lesions of the cauda equina and the brachial plexus when sufficient nerves are present in the muscles so that these muscles do not manifest electrical signs of complete denervation but the intact nerves are too few to furnish sufficient energy for voluntary motion.

ALPERS, Philadelphia.

PERIPHERAL FACIAL PALSY: MULTIPLE ATTACKS IN THREE BROTHERS. T. T. STONE, J. A. M. A. **143**:1154 (July 29) 1950.

Stone reports peripheral paralysis of the seventh cranial (facial) nerve occurring in several attacks of this type of palsy in each of three brothers. One of the brothers also had two attacks of external ophthalmoplegia. The father of the patients had attacks of peripheral paralysis of the left facial nerve three years and one year after the facial paralysis experienced by the first and second sons, respectively, and one year before that of the third son. Stone raises the question whether these paralyses were due to a hereditary or a familial factor.

ALPERS, Philadelphia.

IMPAIRED VIBRATORY SENSE IN DIABETES MELLITUS WITH PROTEINURIA. W. S. COLLENS, J. D. ZILINSKY, L. C. BOAS, and J. J. GREENWALD, J. Clin. Invest. **29**:723 (June) 1950.

The use of an electrically activated tuning fork has served as a satisfactory tool for quantitating vibratory sense. By this method it was found that diabetic subjects almost invariably revealed an impairment in transmission of vibration-sensory impulses. It was also observed that the degree of impairment varied widely among these patients. Diabetic patients with renal complications were most seriously affected. In a study of 100 diabetic patients with proteinuria there was a much more profound impairment in vibration sense than in 100 diabetic patients without proteinuria.

The interesting coexistence of more advanced neuropathy with proteinuria is a basis for speculating as to whether a kidney through which protein is being lost from the body is also permeable to members of the vitamin-B complex, possessing antineuritic properties. On the other hand, the condition that makes for a disturbance in the metabolism of the peripheral nerve may also make for increased permeability of the kidney to protein.

ALPERS, Philadelphia.

INTRADURAL LIPOMA OF THE SPINAL CORD. L. BARRAQUER-FERRÈ, E. TOLOSA, L. BARRAQUER-BORDAS, and F. DURÁN, Acta psychiat. et neurol. **25**:7, 1950.

Intradural lipoma of the spinal cord is uncommon. Altogether, 35 cases are available for symptomatologic analysis. Other cases have simply been tabulated in the general statistics.

The authors report a case of intradural lipoma of the spinal cord in a man aged 21. The clinical picture was characterized by a posterior-column syndrome, absence of root pain, and widening of the spinal canal. There were spastic paraparesis and a sensory level, with albuminocytologic dissociation, manometric block, and arrest of descending iodized oil. The patient had pes cavus (*pied creux*) and morphologically abnormal thorax. Surgical subtotal extirpation resulted in good recovery from the motor and sensory disturbances.

ALPERS, Philadelphia.

Treatment, Neurosurgery

STREPTOMYCIN IN TREATMENT OF PROTEUS VULGARIS MENINGITIS. L. ROSOE, H. E. WEST, and A. G. BOWER, Ann. Int. Med. **32**:960 (May) 1950.

The authors report two cases in which Proteus-vulgaris meningitis was successfully treated with streptomycin by the intrathecal and intramuscular routes. Streptomycin, and possibly

chloramphenicol (chloromycetin®), are believed to be the drugs of choice in the treatment of this condition. The two cases occurred prior to the availability of chloramphenicol. Early surgical intervention in cases of known foci of infection is indicated in the management of this condition.

ALPERS, Philadelphia.

USE OF 3, METHYL, 5, PHENYLHYDANTOIN (AC114) IN THE TREATMENT OF EPILEPSY: A PRELIMINARY REPORT. S. LIVINGSTON and A. Y. SWEET, Bull. Johns Hopkins Hosp. **86**:359 (June) 1950.

This study deals with a group of 42 patients who were treated with AC114. Twenty-seven of these patients had been receiving one or more of the usual forms of therapy for at least one year before AC114 was started. In each instance the previous medication had proved ineffective. Each of these patients was treated with AC114 plus their previous ineffective medication. The remaining 15 patients had been observed for at least six months but did not receive regular anticonvulsant medication. Each of these patients was treated with AC114 alone.

Livingstone and Sweet found that AC114 was effective only in controlling grand ural convulsions. Twenty-five, or 60% of the total group of patients, were either completely controlled or improved. AC114 was found to be effective in a number of instances in which other drugs had not given adequate control. It was also used in conjunction with other drugs, and no evidence of incompatibility was encountered. In addition to its apparent anticonvulsant value, AC114 appears to possess low toxicity and little sedative effect.

ALPERS, Philadelphia.

DEATH FOLLOWING ELECTROSHOCK TREATMENT. J. M. NIELSEN, Bull. Los Angeles Neurol. Soc. **15**:200 (Sept.) 1950.

A woman aged 51 was seen in her third attack of "trifacial neuralgia." The first attack occurred at the age of 39. The second, at the age of 45, was much severer. She had been depressed during both attacks, and during the second she was treated with 12 electric-shock convulsions. When seen in the third attack, she complained of constant, severe pain. She obtained only brief relief with various measures and gradually showed deepening depression with severe agitation. Electric-shock treatments were recommended.

The patient was in good physical condition when electric-shock therapy was begun in a sanatorium. After the third treatment she stated that her pain was almost gone. In a much improved emotional state, she accepted the fourth treatment. She reacted as usual during treatment but did not awaken as expected. Her temperature was taken and found to be 108 F. She was in profound shock. In spite of treatment instituted immediately, she died 24 hours after the electric-shock treatment, without having regained consciousness.

Autopsy showed that "there were localized areas of subcortical necrosis of the cerebral hemispheres, and early neural degeneration and chromatolysis of the subcortical region of the cerebral hemispheres and basal ganglia. There were fatty changes throughout the liver and mild congestion of the liver, lungs, spleen and kidneys."

Nothing was found in the brain stem of the hypothalamus, where a lesion was expected. What relation the changes bore to death is not clear. The patient spoke well and was clearly oriented immediately before the treatment, and the probability is that the cerebral changes developed in the remaining 24 hours of life. The patient died of hyperthermia, but why it developed is not clear.

ALPERS, Philadelphia.

ORALLY GIVEN MEPHENESIN IN INFANTILE CEREBRAL PALSY. C. H. FRANTZ, J. A. M. A. **143**:424 (June 3) 1950.

Frantz found that orally given mephenesin (tolserol®) was well tolerated over a seven-month period by 23 children (86%) of a test group of 27 subjects with infantile cerebral palsy. The ages of the subjects varied from 3 to 21 years. Children over 10 years of age seemed to respond better than the younger subjects.

No undesirable effects were manifest in studies of the blood and urine. Vertigo, nausea, vomiting, irritability, and listlessness were undesirable side effects noted in children receiving doses up to 2 gm. Vertigo in most cases was easily controlled by a change in dosage.

Children with spasticity and rigidity did not respond satisfactorily in the group evaluated. Of 16 athetoid children, 14 (87%) demonstrated beneficial effects. Children with tension athetosis seem to have a favorable response to mephenesin more consistently than did other groups.

ALPERS, Philadelphia.

NEUROTOXIC REACTIONS TO DIHYDROSTREPTOMYCIN. D. T. CARR, H. A. BROWN, C. H. HODGSON, and F. R. HEILMAN, J. A. M. A. **143**:1223 (Aug. 5) 1950.

Dihydrostreptomycin was recently introduced as a substitute for streptomycin, the main advantage being that the new drug is less neurotoxic. However, both laboratory and clinical studies emphasized the fact that the new drug was not completely free of neurotoxicity and that its use might be followed by impaired vestibular function or deafness or both.

In an effort to learn why certain patients had untoward reactions, the authors reviewed the records of 10 patients with neurotoxic reactions to dihydrostreptomycin. In nine of the 10 cases there was either direct or circumstantial evidence that the maximal concentration of dihydrostreptomycin in the blood serum was greater than 60 γ per cubic centimeter. Although the maximal safe concentration of dihydrostreptomycin in the blood serum is not known, it seems likely that a maximal daily concentration of more than 60 γ per cubic centimeter for several weeks frequently damages either the vestibular or the auditory system.

ALPERS, Philadelphia.

CHLORAMPHENICOL IN THE TREATMENT OF HEMOPHILUS INFLUENZAE MENINGITIS. G. W. PRATHER, and M. H. D. SMITH, J. A. M. A. **143**:1405 (Aug. 19) 1950.

Chloramphenicol has been found to be very active against Hemophilus pertussis and Hemophilus influenzae in vitro. It readily passes into the spinal fluid, where it reaches concentrations ranging from 30 to 50% of that in the blood. These facts led the authors to try the drug in a series of 15 consecutive unselected cases of meningitis due to H. influenzae type B. Eight of the patients were under 1 year of age. In every case the spinal fluid was sterile on the second lumbar puncture, performed within an average interval of 21 hours. No toxic effects attributable to the drug were observed. All the patients recovered.

Optimal dosage schedules remain to be worked out. Prather and Smith suggest 50 or 100 mg. per kilogram of body weight administered by mouth or by stomach tube on admission, followed by 250 mg. every eight hours thereafter for five or more days, regardless of weight.

ALPERS, Philadelphia.

CORTISONE IN SYDENHAM'S CHOREA. N. ARONSON, H. S. DOUGLAS, and J. M. LEWIS, J. A. M. A. **145**:30 (Jan. 6) 1951.

The authors report two cases of chorea in children who were treated with cortisone and failed to show a favorable response. The first case was that of a child of 3 years who had had weakness and choreic movements for four weeks. Two weeks before therapy, fever and erythema multiforme appeared for two days. At this time the sedimentation rate was 38 mm. in one hour. At the time the patient was seen there were generalized weakness and continuous movements. There was a soft systolic murmur, but the heart seemed otherwise normal. The sedimentation rate at this time was 3 mm. in one hour. The 24-hour urinary excretion of 17-ketosteroids was 1.8 mg. A total dose of 0.975 gm. of cortisone was administered over a 14-day period. The patient's clinical status was unchanged throughout this two-week period. The only laboratory change noted was an increase in the urinary excretion of 17-ketosteroids, from 1.8 (in 24 hours) to 4.3 mg.

The second case was that of a boy of 9 years who had been ill only five days, with choreiform movements and some weakness of the hands. On the fourth day in the hospital erythema multiforme developed and lasted about 10 days. During this time the patient was afebrile, although the sedimentation rate ranged from 27 to 45 mm. Cortisone was started on the ninth day in the hospital, and total dose of 2.175 gm. was given over a 20-day period. The symptoms of chorea during this time, however, became progressively more intense.

Administration of corticotropin (ACTH) was started on the day the cortisone therapy was stopped, a total of 0.925 gm. being given over a period of nine days. It was considered that

the slight improvement noted during the administration of the drug was unrelated to therapy, mild to moderate chorea being still present.

The significant laboratory findings were a reduction in the sedimentation rate from 19 mm. (under cortisone therapy) to 2 mm. (under ACTH); a decrease in the eosinophil count from the original 263 per cubic millimeter to 62 (under cortisone) to 0 (with corticotropin); an increase in 17-ketosteroids from 5 mg. (in 24 hours) to 11.9 mg. (with cortisone) to 23.6 mg. (with corticotropin).

ALPERS, Philadelphia.

SURGICAL TREATMENT OF ARNOLD-CHIARI MALFORMATION IN ADULTS. W. J. GARDNER and R. J. GOODALL, J. Neurosurg. **7**:199 (May) 1950.

The Arnold-Chiari malformation is a deformity of the hindbrain in which a tongue-like projection of the cerebellar tonsils protrudes through the foramen magnum down onto the cervical portion of the spinal cord. The caudad portion of the fourth ventricle likewise is elongated downward. The upper cervical nerve roots pursue a cephalad direction, giving the impression that the brain stem has been drawn through the foramen magnum.

Gardner and Goodall have operated on 17 patients, adults and adolescents, with the Arnold-Chiari malformation, and their experience suggests that the fundamental mechanism is obstructive hydrocephalus with resulting foraminal herniation of the hindbrain.

The authors believe that the "congenital" form of platybasia is produced by the increased weight of the head and the malleability of the skull bones in cases of congenital obstructive hydrocephalus. On the other hand, if the infant is unable to assume the erect posture because of an associated myelomeningocele, platybasia should not develop. In acquired platybasia of Paget's disease (osteitis deformans), osteogenesis imperfecta, and other bone-softening disorders, an Arnold-Chiari-like deformity results from the extrusion of the hindbrain through the foramen magnum, owing to the encroachment on the volume of the brain case occasioned by the deformity. While this may resemble the congenital variety of true Arnold-Chiari deformity, it is not accompanied by hydrocephalomyelia.

The Arnold-Chiari malformation should be suspected in any patient with signs suggesting syringomyelia, syringobulbia, platybasia, or the Klippel-Feil syndrome, and also in a patient with unexplained scoliosis. It should be particularly suspected in cases of the above-mentioned conditions if cerebellar signs are present or if there is impairment of pain perception in the distribution of the second cervical nerve. The diagnosis may be confirmed in these cases by encephalography. The roentgenograms will disclose evidence of obstructive hydrocephalus, with absence of air in the cisterna magna. Since the intraventricular pressure is usually only slightly increased, this procedure is safe, provided the surgeon is prepared to operate at once if the roentgenogram confirms the diagnosis. Surgical treatment should be aimed at relief of the obstructive hydrocephalus.

In this series of 17 patients, 13 were definitely benefited by the operation, 3 were made worse because of aggravation of quadriparesis, and 1 died 18 hours after operation, of respiratory failure.

ALPERS, Philadelphia.

RESULTS OF 300 PITUITARY ADENOMA OPERATIONS (PROF. HERBERT OLIVECRONA'S SERIES). L. BAKAY, J. Neurosurg. **7**:240 (May) 1950.

In this series, 292 patients with verified adenomas of the pituitary were treated and 300 operations performed. This represented 8.9% of the total number of verified brain tumors in the Olivecrona series. The series included 232 chromophobic, 55 acidophilic, 2 basophilic, and 3 malignant adenomas.

The surgical approach was transfrontal in 241 cases of chromophobic and 45 cases of acidophilic adenoma (95.3% of all operations), and transsphenoidal in 5 cases of chromophobic and 9 cases of acidophilic adenoma (4.7%).

The postoperative mortality rate was 11.3% for the chromophobic and 9.5% for the acidophilic adenomas. There was a striking difference, however, between the group of intrasellar tumors and the group with extrasellar extension, the first having a mortality rate of 6.4% and the second, a rate of 35.0%.

Cases of adenoma with extension in the cavernous sinus, Meckel's cavity, temporal lobe, hypothalamus, or third ventricle were included. Those in which there was extension in the cavernous sinus did not reveal a higher postoperative mortality rate than in cases of the usual adenoma. There were more fatalities among patients with hypothalamic signs, and the late results of operation were not favorable.

The ophthalmic and endocrine symptoms and the effect of removal of the pituitary adenomas thereon are discussed.

Two years after operation or later, 54.5% of the surviving patients with chromophobic adenoma were fully able to work; the ability was reduced in 27.2% of the patients and lost in 8.3%. Of the acromegalic patients, the late postoperative ability to work was complete in 56.6%, reduced in 23.3%, and lost in 13.3%. Radical transfrontal removal of the adenomas and postoperative x-ray treatment in this series were followed by long survival periods and relatively few recurrences.

There were 16 operations for recurrence of the adenoma. The mortality rate after secondary procedures was less than that after primary operations, and the time of survival was usually long. The late results, however, were less favorable in regard to ability to work. Recurrence rates of 10 to 15% for the chromophobic, and of about 20% for the acidophilic, adenomas are estimated.

ALPERS, Philadelphia.

ANTABUSE: CONTRA-INDICATION TO ITS USE. V. P. NORMAN and F. DRUSINSKY, South African M. J. **24**:152 (March 4) 1950.

According to Norman and Drusinsky, the treatment of alcoholism with tetraethylthiuram disulfide (antabuse®) requires caution. Patients with diabetes are a bad risk, because the increased concentration of acetic aldehyde in the blood may precipitate coma. The authors cite the case of a man aged 35 in whom a pronounced optical systolic bruit and a faint blowing aortic diastolic murmur developed. An electrocardiogram revealed evidence of supraventricular tachycardia with slurring of the T wave in lead II depressed RS-T segment in lead III and inversion of the T wave in lead III. Lead IV also showed a depressed RS-T segment complex. These changes are all suggestive of cardiac ischemia. Patients with demonstrable cardiac lesions and angina of effort should not be given this drug.

J. A. M. A.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

Michael Scott, M.D., Presiding
Regular Meeting, March 2, 1951

Posterior-Inferior Cerebellar Artery Syndrome in a Man Aged 20. Dr. George Wilson, Dr. A. M. Ornsteen, and Dr. W. Sagen (by invitation).

The usual cause of the posterior-inferior cerebellar artery syndrome is thrombosis associated with arteriosclerosis with or without hypertension, and the usual age of occurrence is in the sixth decade of life or later. The etiologic agent in cases which occur in younger persons is syphilis, subacute bacterial endocarditis, or embolism secondary to other situations. Other etiologic factors reported in the literature include (1) aneurysm of the posterior inferior cerebellar artery; (2) tumor, primary in the area of supply of this artery, and also metastatic; (3) Hodgkin's disease, and (4) tuberculoma.

A case of the syndrome in a man aged 20 was reported in which none of these agents could be implicated. The causes considered were (1) multiple sclerosis and (2) localized encephalitis. No case of this syndrome occurring with either of these diseases was found in the literature.

DISCUSSION

Dr. A. M. Ornsteen: It seemed worth while to present this case, if for no other reason than the fact that the appearance of this syndrome at the age of 20 is unusual. Because the presence of hiccups and a history of somnolence and fever, we suspected encephalitis. Multiple sclerosis had to be considered, but none of us recalled having seen this syndrome in association with that disease. In a personal communication, Dr. Robert Wartenberg mentioned its occurrence, and I have written to him to learn the source of his information. We have not clearly established the cause, but I think we are justified in suspecting multiple sclerosis, particularly in view of the history of remissions.

Dr. Alexander Silverstein: I remember a case in which this syndrome developed after an operation in early adult life and seven years later the presence of multiple sclerosis became clear. The diagnosis seems fairly certain in the present case. Several years ago I reviewed 70 cases in the pathology laboratory at Philadephia General Hospital in which the clinical diagnosis of encephalitis had been made. In none of them was there any pathological evidence of this condition. In 90% of that series tumor was the etiologic agent. I feel that the diagnosis of encephalitis is a questionable one.

Dr. E. A. Denbo: In your review of the literature, Dr. Sagen, did you encounter any cases in which hemorrhage would produce this syndrome?

Dr. Michael Scott: I recall the case at Temple University Hospital of a young man who had had malaria in the Army. Could malaria possibly have been a cause of the syndrome in this young person?

Dr. William Sagen (by invitation): I discovered no cases in the literature of hemorrhage alone as a primary cause of this syndrome. It does, of course, occur secondary to thrombosis or tumor in the area affected.

Cerebral Fat Embolism. Dr. Alexander Silverstein and Dr. Luke Jordan (by invitation).

A white man aged 79 was struck by an automobile on Feb. 13, 1949 and was admitted to the Philadephia General Hospital with fractures of the pelvis and the neck of the right femur. He was mentally clear for one hour and then lapsed into unconsciousness.

Examination revealed rigidity of all the extremities, with a Babinski sign on the left. The following day the patient remained comatose, with decerebrate rigidity and intermittent tonic fits.

The appearance of petechiae in the conjunctivas and over the chest established the diagnosis of cerebral fat embolism. A roentgenogram of the lungs showed changes which were interpreted as multiple infarcts. On the third day sizzle tests for fat in the urine were positive, becoming strongly positive on the fourth day, when the patient died.

Medical and surgical consultants failed to suspect fat embolism as a factor; a neurosurgeon believed that the clinical picture was due to cerebral trauma and suggested "watchful waiting."

The principal lesions in the brain were (1) petechial hemorrhages, (2) areas of rarefaction, (3) areas of demyelination, and (4) fat in the lumen of vessels with perivascular demyelination. All these lesions were widespread but were present chiefly in the subcortex, basal ganglia, and brain stem.

From the study of this case, as well as experience with similar cases, we believe that cerebral fat embolism should be considered a possibility after trauma.

DISCUSSION

DR. ALEXANDER SILVERSTEIN: I first brought up the subject of fat embolism before this society in 1938, when the members were inclined to be somewhat incredulous, and some still are. The orthopedic department at Temple University has become impressed with the importance of the condition, however, and has cooperated with me in carrying on my studies of this condition. I believe that fat embolism is still overlooked as a possibility in many cases of head injury. The diagnosis does not appear on the records at Temple University Hospital before 1939, and we have had seven cases since 1944. It certainly should be considered a possibility in cases of unfavorable reactions to electric shock and metrazol® treatments. In England, it has been pointed out that cerebral fat embolism also occurs after blast injuries, an observation which may make it important to remember the diagnosis if we are attacked with atomic bombs. I suspect the condition is frequently overlooked post partum, for neuropathologists do not routinely use fat stains.

DR. A. M. ORNSTEEN: It is difficult for me to understand how the fat gets through the pulmonary plexus of capillaries into the arterial circulation. It is my opinion that the incidence of this condition is not high.

DR. MATTHEW MOORE: It has been well established, by many experiments, that fat can get through the pulmonary capillaries.

DR. SHERMAN F. GILPIN: I agree that the condition should be searched for more frequently than it has been, but I do not feel that the occurrence of seven cases at Temple University since 1944 establishes it as a very important problem clinically.

DR. ALEXANDER SILVERSTEIN: It is certainly true that fat can pass through the capillaries of the pulmonary circulation, but other mechanisms are possible. Products from traumatized tissue may alter the chemistry of the blood colloids, to lead to the formation of fat globules in various parts of the body. It is also possible that fat, by its irritative qualities, may alter the blood chemistry so that the deposit of globules can occur without the fat actually being transported as globules through the pulmonary circulation. I believe that both deposit and transport may account for the appearance of fat emboli in the nervous system.

Clinical Value of the Thumb Position in Diagnostic Screening. DR. TEMPLE FAY.

The thumb, its function and position, marks one of the distinguishing anthropological characteristics of man. Its large cortical representation, its varied function, and its triple nerve supply make it an excellent structure to test and observe for the purpose of differential diagnosis.

Nine clinical signs which have been found to be an aid in diagnostic screening of paralyses of the brain, cord, and peripheral nerve type were presented.

"Cortical" Thumb.—In spastic types of paralysis the thumb is drawn into the palm (lesions above the fifth cervical level).

"Midbrain" Thumb.—Slow, dyskinetic movements of the thumb to the ball of the index finger are seen in Parkinsonism (the striatal level).

"Cerebellar" Thumb.—By having the patient touch the tip of the thumb to the tip of the nose, the presence of intention tremor may be detected.

"Cord" or "Amyotrophic" Thumb.—In lesions of the cord, the tip of the thumb can be placed over the knuckle, at the base of the index finger.

"Radial Nerve" Thumb.—The tip of the thumb cannot be held in the "cock-up" position, owing to paralysis of extensors of the wrist and thumb.

"Median Nerve" Thumb.—The patient cannot appose the thumb to any one of the fingers or flex or abduct it.

"Ulnar Nerve" Thumb.—The patient is unable to touch the tip of the little finger to the tip of the thumb.

"Flaccid" Thumb.—As a result of a lesion of the brachial plexus, cord, or cortex, the thumb has no remaining movement.

"Fixed" Thumb.—This may be due to such conditions as joint involvement, contracture, injury, bone disease or arthritis.

The importance of the human thumb in military neurological screening in separate tentatively cranial, spinal, and peripheral types of lesions, was emphasized.

DISCUSSION

DR. A. M. ORNSTEEN: It was not clear to me how the position of the thumb could localize a lesion at the high cervical level of the cord, above the segments which supply the thumb directly. The rest of the statements in this paper are characteristic of Dr. Fay's careful and critical analysis of minutiae.

DR. HENRY T. WYCIS: We have been taught that patterns of movement laid down in the cortex control groups of muscles, not single muscles. This is not true with electrical stimulation, which produces movements in single muscles. To be sure, electrical stimuli are not physiological; but I should like to have Dr. Fay comment on this problem.

DR. TEMPLE FAY: I did not present this paper as an original contribution, but it is important to emphasize this diagnostic approach when one is faced with the need for rapid screening. By observing carefully the position of the thumb when a patient comes in, it is often possible to localize his lesion at first glance. Localization in the high cervical portion of the cord would be possible if no cranial-nerve signs pointed to extension of the process above this level and if the abnormalities in the thumb were obviously the result of upper-motor-neuron disease. In answer to Dr. Wycis' question, I doubt whether the cortical points we stimulate electrically ever act alone in life. Certainly, in rehabilitation one can put the patterns together, but one cannot break them up into single-muscle responses.

Electroencephalographic Changes in Parkinsonism. DR. AARON W. MALLIN, DR. ISADORE ROSE (by invitation), and DR. JOSEPH HUGHES (by invitation).

Thirteen unselected cases of postencephalitic and arteriosclerotic Parkinsonism from the neurological wards of the Philadelphia General Hospital were studied clinically and electroencephalographically. The etiology, clinical picture, and gross and microscopic pathology of the Parkinsonian syndrome were summarized. The anatomical relations of the basal ganglia, thalamus, cortex, and various extrapyramidal projection systems were delineated. Mention was made of subcortical influences on cortical electrical activity and the various hypotheses concerning the electroencephalographic frequency, as well as the role of the reticular systems of the thalamus. The theories concerning the neurophysiology of Parkinsonian tremor were discussed. The literature on electroencephalographic patterns in acute and chronic encephalitis was reviewed, and the conflicting opinions were briefly noted. Movement artefacts have been blamed in some reports for the abnormalities noted.

The abnormalities in six cases were demonstrated by slides. Electroencephalographic abnormalities were present in all 13 cases of the series, and were diffuse in both hemispheres, particularly the frontal and parietal areas. In the authors' opinion, they were not explained by artefacts. Lesions known to be scattered through the reticular activating systems of the diencephalon were offered as explanation for the changes noted.

DISCUSSION

DR. JOSEPH HUGHES (by invitation): I wish to mention two points: First, it is significant that clinically these lesions are known to be diffuse, so that one might expect asynchronous records from disturbance of the feed-back circuits. Second, the severity of the illness in the patients we used accounts for the greater incidence of abnormal records.

DR. ISADORE ROSE (by invitation): I want to emphasize that in our series 100% of the records showed abnormalities.

DR. HENRY T. WYCIS: How is it possible to suppress the tremors and avoid artefacts so successfully in these patients? Jasper's work, which was cited, must be evaluated in the light of the fact that he was working on cats, not human beings. Dr. Bucy has agreed with me recently that his diagrams require revision in the light of the work Dr. Spiegel and I have been doing with lesions in the globus pallidus. Were his diagrams correct, these lesions should make the tremor worse; but they do not. The lesions are obviously diffuse, and therefore no single operation will correct the condition.

DR. TEMPLE FAY: Since the tremors of Parkinsonism disappear during sleep, I wonder whether it would be worth while to try the effect of hyperventilation, as well as that of changing the carbon-dioxide intake, which may conceivably be related to the changes observed in sleep. I myself prefer to accept the concept that these tremors are release phenomena rather than the result of irritation or overstimulation. The characteristic pill-rolling movement has certain interesting analogies to the movement of a fish's fin and may well represent the removal of inhibition from a primitive center in which this old pattern is preserved. In this connection, could the abnormal cortical waves represent release by lower levels?

DR. AARON MALLIN: I can only say that the freedom of the records from artefacts reflects the skill of our technicians and that we, too, were surprised to find how few artefacts we encountered. In answer to Dr. Fay's question, I should point out that all these patients were subjected to hyperventilation, which did increase the abnormalities. Studies with carbon dioxide and during sleep are certainly worth considering and may yet be done.

DR. JOSEPH HUGHES: I should like to pay tribute to the work being done by Dr. Spiegel and Dr. Wycis, since their method permits us to learn about this condition in human beings, rather than having to rely on analogies with cats and monkeys. In reply to Dr. Fay, I think that we must recognize that there is some change in the fashion of the times. Many of us now prefer to think in terms of feed-back circuits, rather than in terms of special nuclei which are released in this condition.

News and Comment

MEDICAL MOTION PICTURES

A revised catalogue of motion pictures available through the Committee on Medical Motion Pictures of the American Medical Association is now ready. Copies will be sent to the secretary of each county and state medical society. This catalogue lists 62 16-mm. films, most of which are at the professional level. Fourteen of these films are suitable for showing to lay groups. Eight new films have been added. Copies are available upon request from the Committee on Medical Motion Pictures, American Medical Association, 535 No. Dearborn St., Chicago 10.

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Neurology and Psychiatry.—Eli Robins, St. Louis.

* The asterisk denotes supplementary certification.

Book Reviews

Introduction to a Psychoanalytic Psychiatry. By Paul Schilder, M.D., Ph.D. Translated by Bernard Glueck, M.D. Price, $3.25. Pp. 178. The International Universities Press, Inc., 227 W. 13th St., New York 11, 1951.

More than 25 years after its first German edition, Paul Schilder's "Introduction to a Psychoanalytic Psychiatry" is brought out in unchanged version by the International Universities Press, Inc., New York. Reading this book again shows how much psychodynamic thinking has progressed in these years, especially in the concept and treatment of the schizophrenic psychoses. Such progress does not distract from the fact that this book was always considered a landmark in the historical development of psychodynamic psychiatry and still lives up to its title—to be a first attempt at a systematic presentation of the clinical psychiatry on a psychoanalytic basis. This book is of great value, and a psychiatric library without it would be incomplete. The wide field of topics under discussion ranges from the general introduction to special problems of schizophrenia and other functional psychoses. It also includes an analytic discussion of problems concerning dementia paralytica, Korsakoff's disorder, epilepsy, toxic psychoses, and other organic types of reactions.

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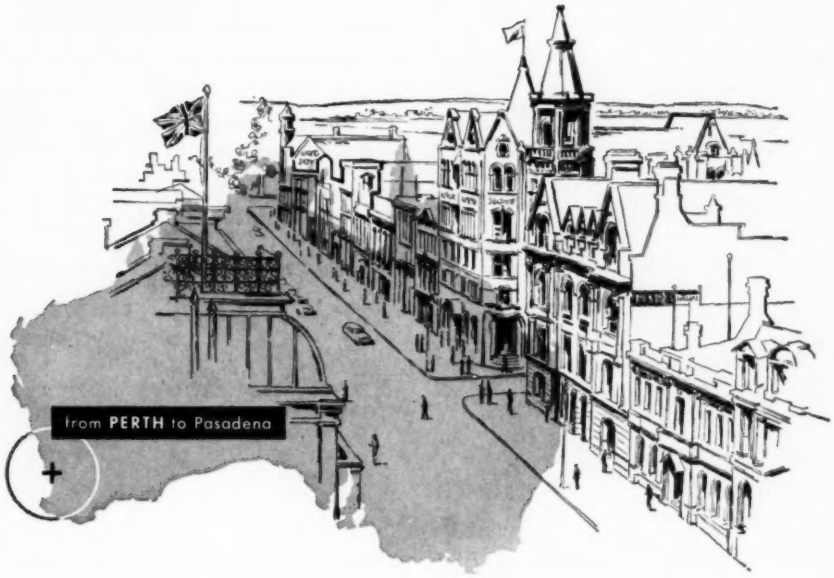

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